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I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003901873 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. as filed on 31 March 2003.

WITNESS my hand this
Second day of December 2003

J. Billingsley

JULIE BILLINGSLEY
TEAM LEADER EXAMINATION
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Regulation 3.2

Fujisawa Pharmaceutical Co., Ltd.

A U S T R A L I A

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"Inhibitor of Cox"

The invention is described in the following statement:

D E S C R I P T I O N

INHIBITOR OF COX

TECHNICAL FIELD

This invention relates to new compounds and pharmaceutically acceptable salts thereof having pharmacological activity.

Moreover, this invention relates to medicament or pharmaceutical composition comprising the above mentioned new compounds or pharmaceutically acceptable salts thereof as an active ingredient for treatment and/or prevention of inflammatory conditions, various pains, and so on.

BACKGROUND ART

Cyclooxygenase catalyzes early stage reaction of arachidonate cascade, which is very important for a living body. For example, this cascade synthesizes prostaglandins as autacoids. So, antagonists or agonists of cyclooxygenase can be expected as medicines for treatment and/or prevention of inflammatory conditions, and so on.

As this cyclooxygenase, the presence of two isoenzymes, cyclooxygenase-I (COX-I) and cyclooxygenase-II (COX-II), is known (Proc. Nat. Acad. Sci. USA, 88, pp.2692-2696 (1991)). COX-I is always expressed over whole body and participates the maintenance of biological function at various tissues. On the other hand, COX-II is not always expressed and is induced by tumor promoter, growth factor,

cytokine, or the like.

Traditional non steroidal anti-inflammatory compounds (NSAIDs) have inhibiting activities of both COX-I and COX-II (J. Biol. Chem., 268, pp.6610-6614 (1993), etc). So, the therapeutic use thereof involves undesired effects on the gastrointestinal tract, such as bleeding, erosions, gastric and intestinal ulcers, etc.

It was reported that selective inhibition of COX-II shows anti-inflammatory and analgesic activities comparable with conventional NSAIDs but with a lower incidence of some gastrointestinal undesired effects (Pro. Nat. Acad. Sci. USA, 91, pp.3228-3232(1994)). Accordingly, various selective COX-II inhibitors have been prepared.

However, it was also reported that those "selective COX-II inhibitors" show some side-effects on kidney and/or insufficient efficacy on acute pains.

Therefore, some compounds such as SC-560, mofezolac, etc., which have certain selective inhibiting activity against COX-I, have been researched. WO98/57910 shows some compounds having such activity. However, their selectivity of inhibiting COX-I does not seem to be enough to use them as a clinically acceptable and satisfactory analgesic agent due to their gastrointestinal disorders.

Further, WO02/055502 shows some pyridine derivatives having cyclooxygenase inhibiting activity, particularly cyclooxygenase-I inhibiting activity. And WO99/51580 shows some triazole derivatives having an inhibiting activity of cytokine production.

However, the compounds, which have further superior

selective COX-I inhibiting activity, have been expected.

DISCLOSURE OF THE INVENTION

As a result of studies on the synthesis of new compounds and their pharmaceutical activity, the inventors of this invention have found that the new compounds of this invention have superior activity of inhibiting COX (especially, COX-I inhibiting activity). So, this invention relates to new compounds, which have pharmaceutical activity such as COX inhibiting activity, to a medicament and a pharmaceutical composition containing the new compounds.

Accordingly, one object of this invention is to provide the new compounds, a medicament, and a pharmaceutical composition, which have a COX inhibiting activity (especially, COX-I inhibiting activity).

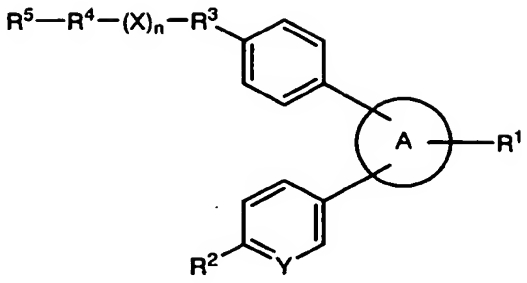
Another object of this invention is to provide a method for treatment and/or prevention and the new compounds for use as medicament in the treatment and/or prevention of the disease associated with COX.

A further object of this invention is to provide a use of the new compounds for manufacturing a medicament for treating or preventing the diseases and the analgesic agent comprising the new compounds which is usable for treating and/or preventing pains.

A further object of this invention is to provide the commercial package comprising the pharmaceutical composition containing the new compound.

Th new compounds of this invention can be represented

by the following general formula (I):



(I)

wherein

R^1 is (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkyl substituted with substituent(s) (i) described later, [(lower)alkoxy]carbonyl, carbamoyl, carbamoyl substituted with substituent(s) (ii) described later, cyano, (lower)acyl, aryl, aryl carbonyl, carboxy, or cycloalkyl;

R^2 is (lower)alkyl, (lower)alkoxy, cyano, or heterocyclic group;

R^3 is (lower)alkylene, (lower)alkenylene, or covalent bond;

R^4 is (lower)alkylene, (lower)alkenylene, or covalent bond;

R^5 is hydrogen, aryl, hydroxy, [(lower)alkoxy]carbonyl, cyano, amino, [(lower)acyl]amino, [(lower)alkoxy]carbonylamino, carbamoylamino, [(lower)acyl]oxy, [(lower)alkyl]sulfonyloxy, heteroaryl, or [(lower)alkyl]sulfonylamino;

X is "O", "S", "SO", or "SO_2";

Y is "CH" or "N";

n is 0 or 1;

is oxazolyl group;

substituent(s) (i) is(are) selected from the group consisting of (lower)alkoxy, hydroxy, halogen, aryl[(lower)alkyl]oxy, [(lower)alkoxy]carbonyl, carboxy, [(lower)acyl]oxy, and aryl; and

substituent(s) (ii) is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, and in case that carbamoyl is substituted with two (lower)alkyls they may be cyclized together;

or pharmaceutically acceptable salts thereof.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

So, the "(lower)alkyl" means a straight or branched chain aliphatic hydrocarbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isoamyl, hexyl, and the like, and it is preferably (C1-C4)alkyl, more preferably (C1-C2)alkyl, most preferably methyl.

The "(lower)alkenyl" means a straight or branched chain aliphatic hydrocarbon having more than one double

bond between two carbon atom, such as ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, hexenyl, and the like, and it is preferably (C2-C4)alkenyl, more preferably (C2-C3)alkenyl.

The "(lower)alkynyl" means a straight or branched chain aliphatic hydrocarbon having more than one triple bond between two carbon atom, such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like, and it is preferably (C2-C4)alkynyl, more preferably (C2-C3)alkynyl.

The "(lower)alkoxy" means a straight or branched chain aliphatic hydrocarbon oxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, or the like, and it is preferably (C1-C4)alkoxy, more preferably (C1-C2)alkoxy, most preferably methoxy.

The "[(lower)alkoxy]carbonyl" means a $-CO_2-$[(lower)alkyl] group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, and the like, and it is preferably [(C1-C4)alkoxy]carbonyl, more preferably etoxycarbonyl.

The "(lower)acyl" means a formyl and a (lower)alkyl carbonyl group, such as acetyl, propionyl, butynyl, isobutynyl, valeryl, isovaleryl, pivaloyl, hexanoyl, and the like, and it is preferably (C1-C4)acyl (including formyl), more preferably (C1-C2)acyl, most preferably acetyl.

The "aryl" means an aromatic hydrocarbon group, such

as phenyl, naphtyl, indenyl, or the like, and it is preferably (C6-C10)aryl, more preferably phenyl.

The "aryl carbonyl" means a carbonyl group substituted with aryl group mentioned above, such as benzoyl, naphtylcarbonyl, indenylcarbonyl, or the like, and it is preferably [(C6-C10)aryl]carbonyl, more preferably benzoyl.

The "cycloalkyl" means C3-C10 cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, and the like, and it is preferably C3-C6 cycloalkyl, more preferably C3-C5 cycloalkyl, most preferably cyclopropyl.

The "heterocyclic group" means 5- or 6-membered saturated heterocyclic group which contains at least one hetero atom such as nitrogen, oxygen, or sulfur atom. The "heterocyclic group" may include 5-membered heterocyclic group such as pyrrolidinyl, imidazolidinyl, pyrazolidyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidyl, isoxazolidyl, thiazolidyl, isothiazolidyl, or the like; and 6-membered heterocyclic group such as piperidyl, piperazinyl, tetrahydropyranyl, pentamethylene sulfide, morpholinyl, or the like.

The "(lower)alkylene" means a straight or branched chain aliphatic hydrocarbon divalent group, such as methylene, ethylene, propylene, methylethylene, butylene, methylpropylene, dimethylpropylene, pentylene, hexylene, and the like, and it is preferably (C1-C4)alkylene, more preferably (C1-C3)alkylene, most preferably (C1-C2)alkylene.

The "(lower)alkenylene" means a straight or branched

chain aliphatic hydrocarbon divalent group having more than one double bond between two carbon atom, such as ethenylene, propenylene, methyleth nylene, butenylene, methylpropenylene, dimethylpropenylene, pentenylene, hexenylene, and the like, and it is preferably (C2-C4)alkenylne, more preferably (C2-C3)alkenylne.

When R^3 or R^4 is "covalent bond" or n is 0, R^3, R^4 or X does not exist. That is, in case that R^3 is "covalent bond", $(X)_n$ group and phenyl group are directly connected as Compound (Ia) described later.

The "[(lower)acyl]amino" means an amino group substituted with (lower)acyl group mentioned above, such as formylamino, acetylamino, propionylamino, butynylamino, isobutynylamino, valerylamino, isovalerylamino, pivaloylamino, hexanoylamino, and the like, and it is preferably [(C1-C4)acyl]amino, more preferably [(C1-C2)acyl]amino, most preferably acetylamino.

The "[(lower)alkoxy]carbonylamino" means an amino group substituted with [(lower)alkoxy]carbonyl group mentioned above, such as methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, isopropoxycarbonylamino, butoxycarbonylamino, isobutoxycarbonylamino, tert-butoxycarbonylamino, pentoxycarbonylamino, hexoxycarbonylamino, and the like, and it is preferably [(C1-C4)alkoxy]carbonylamino, more preferably tert-butoxycarbonylamino.

The "[(lower)acyl]oxy" means an oxygen atom substituted with (lower)acyl group mention d above, such as formyloxy, acetyloxy, propionyloxy, butynyloxy,

isobutynyloxy, valeryloxy, isovaleryloxy, pivaloyloxy, hexanoyloxy, and the like, and it is preferably (C1-C4)acyloxy, more preferably (C1-C2)acyloxy, most preferably acetyloxy.

The "[(lower)alkyl]sulfonyloxy" means a sulfonyloxy group substituted with (lower)alkyl group mentioned above, such as methanesulfonyloxy, ethanesulfonyloxy, propanesulfonyloxy, butanesulfonyloxy, hexanesulfonyloxy, and the like, and it is preferably [(C1-C4)alkyl]sulfonyloxy, more preferably [(C1-C2)alkyl]sulfonyloxy, most preferably methanesulfonyloxy.

The "heteroaryl" means 5-, 6-membered or condensed polycyclic aromatic heterocyclic group which contains at least one hetero atom such as nitrogen, oxygen, sulfur atom. The "heteroaryl" may include 5-membered heteroaryl group such as pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, or the like; 6-membered heteroaryl group such as pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, or the like; and condensed polycyclic aryl group such as indolyl, isoindolyl, isoindole-1,3-dione-2-yl, quinolyl, isoquinolyl, benzofuranyl, chromenyl, benzothienyl, or the like; and is preferably condensed polycyclic aromatic heterocyclic group, more preferably isoindole-1,3-dione-2-yl.

The "[(lower)alkyl]sulfonylamino" means a sulfonylamino group substituted at the sulfonyl group with (lower)alkyl group mentioned above, such as methanesulfonylamino, ethanesulfonylamino,

propanesulfonylamino, butanesulfonylamino, hexanesulfonylamino, and the like, and it is preferably [(C1-C4)alkyl]sulfonylamino, more preferably [(C1-C2)alkyl]sulfonylamino, most preferably methanesulfonylamino.

The "halogen" may include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom, and is preferably a fluorine atom or a chlorine atom, more preferably a fluorine atom.

The "aryl[(lower)alkyl]oxy" means a (lower)alkoxy group substituted with aryl group mentioned above, such as benzyloxy, phenethyloxy, phenylpropyloxy, phenylbutyloxy, naphthylmethyloxy, or the like, and it is preferably aryl[(C1-C4)alkyl]oxy, more preferably aryl[(C1-C2)alkyl]oxy, more preferably phenyl[(C1-C2)alkyl]oxy, most preferably benzyloxy.

The "(lower)alkyl substituted with substituent(s) (i)" means (lower)alkyl substituted with substituent(s) selected from the group consisting of (lower)alkoxy, hydroxy, halogen, aryl[(lower)alkyl]oxy, [(lower)alkoxy]carbonyl, carboxy, [(lower)acyl]oxy, and aryl.

For example, the "(lower)alkyl substituted with (lower)alkoxy" may include methoxymethyl, and the like, and is preferably (C1-C2)alkyl substituted with (C1-C2)alkoxy, more preferably methoxymethyl.

The "(lower)alkyl substituted with hydroxy" may include hydroxymethyl, hydroxyethyl, hydroxypropyl, 1-hydroxyisopropyl, 1-hydroxyisobutyl, 1-hydroxyisoamyl, and the like, and is preferably

1-hydroxy(C1-C6)alkyl.

The "(lower)alkyl substituted with halogen" may include fluoromethyl, chloromethyl, difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, fluoroethyl, chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2,2,3,3,3-pentafluoroethyl, fluoropropyl, fluorobutyl, fluorohexyl, and the like, and is preferably (C1-C4)alkyl substituted with fluorine(s), more preferably (C1-C2)alkyl substituted with fluorine(s), more preferably methyl substituted with fluorine(s), most preferably difluoromethyl or trifluoromethyl.

The "(lower)alkyl substituted with aryl[(lower)alkyl]oxy" may include benzyloxy, and the like.

The "(lower)alkyl substituted with [(lower)alkoxy]carbonyl" may include methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butylcarbonylmethyl, and the like, and is preferably [(C1-C4)alkoxy]carbonyl(C1-C4)alkyl, more preferably [(C1-C2)alkoxy]carbonyl(C1-C2)alkyl.

The "(lower)alkyl substituted with carboxy" may include carboxymethyl, carboxyethyl, carboxybutyl, and the like, and is preferably carboxy[(C1-C4)alkyl], more preferably carboxy[(C1-C2)alkyl].

The "(lower)alkyl substituted with [(lower)acyl]oxy" may include acetoxymethyl, acetoxyethyl, and the like, and is preferably (C1-C4)alkyl substituted with [(C1-C4)acyl]oxy, more preferably (C1-C2)alkyl substituted with [(C1-C2)acyl]oxy.

"The (lower)alkyl substituted with aryl" may include benzyl, phenetyl, and the like.

In case of the number of "substituent(s) (i)" are plural, they may be same or different each other. For example, R^1 may be hydroxy(phenyl)methyl.

In case of the "substituents (ii)" as substituents of carbamoyl group are two (lower)alkyls, they may cyclized together. In that case, R^1 may be 1-pyrrolidinylcarbonyl, 1-piperidylcarbonyl, or the like.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

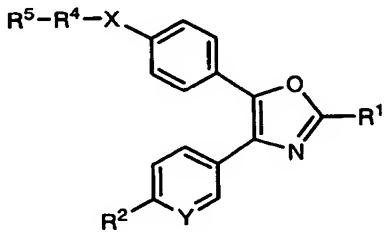
The compounds of the formula (I) and its salts can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

The new compounds of this invention can be converted to salt according to a conventional method. Suitable salts of the compounds (I) are pharmaceutically acceptable conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt,

etc.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, etc.), an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), or the like.

The compound (I) may preferably include a compound of the formula (Ia):



(Ia)

[wherein

R^1 is (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkyl substituted with substituent(s) (i) described later, [(lower)alkoxy]carbonyl, carbamoyl, carbamoyl substituted with substituent(s) (ii) described later, cyano, (lower)acyl, aryl, aryl carbonyl, carboxy, or cycloalkyl;

R^2 is (lower)alkyl, (lower)alkoxy, cyano, or heterocyclic group,

R^4 is (lower)alkylene, (lower)alkenylene, or covalent bond;

R^5 is hydrogen, aryl, hydroxy, [(lower)alkoxy]carbonyl, cyano, amino, [(lower)acyl]amino, [(lower)alkoxy]carbonylamino, carbamoylamino, [(lower)acyl]oxy, [(lower)alkyl]sulfonyloxy, heteroaryl, or [(lower)alkyl]sulfonylamino;

X is "O", "S", "SO", or "SO_2";

Y is "CH" or "N";

substituent(s) (i) is(are) selected from the group consisting of (lower)alkoxy, hydroxy, halogen, aryl[(lower)alkyl]oxy, [(lower)alkoxy]carbonyl, carboxy, [(lower)acyl]oxy, and aryl; and

substituent(s) (ii) is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, and in case that carbamoyl is substituted with two substituents they may be cyclized together].

And in the each definition of the compound formula(I), preferably,

(1) R^1 is (lower)alkyl, (lower)alkyl substituted with substituent(s) (i), [(lower)alkoxy]carbonyl, carbamoyl, carbamoyl substituted with substituent(s) (ii), cyano, (lower)acyl, aryl carbonyl, carboxy, or cycloalkyl,

(2) R^1 is (C1-C4)alkyl, (C1-C4)alkyl substituted with substituent(s) (i), or (C3-C6)cycloalkyl,

(3) R^1 is (C1-C4)alkyl, or (C3-C6)cycloalkyl,

(4) R^1 is (C1-C4)alkyl substituted with substituent(s) (i),

(5) R^1 is [(lower)alkoxy]carbonyl, carbamoyl, carbamoyl substituted with substituent(s) (ii), cyano, (lower)acyl, aryl carbonyl, or carboxy,

(6) R^1 is [(C1-C4)alkoxy]carbonyl, carbamoyl, carbamoyl substituted with substituent(s) (ii), cyano, (C1-C4)acyl, benzoyl, or carboxy,

(7) R^2 is (lower)alkoxy, or cyano,

(8) R^2 is (lower)alkoxy,

(9) R^2 is (C1-C4)alkoxy,

(10) R^3 is (lower)alkylene, or covalent bond,

(11) R^3 is (lower)alkylene,

(12) R^3 is (C1-C4)alkylene,

(13) R^3 is covalent bond,

(14) R^4 is (lower)alkylene, or covalent bond,

(15) R^4 is (lower)alkylene,

(16) R^4 is (C1-C4)alkylene,

(17) R^4 is covalent bond,

(18) R^5 is hydrogen, aryl, hydroxy, [(lower)alkoxy]carbonyl, cyano, amino, [(lower)acyl]amino, [(lower)alkoxy]carbonylamino, carbamoylamino, [(lower)acyl]oxy, [(lower)alkyl]sulfonyloxy, heteroaryl, or [(lower)alkyl]sulfonylamino,

(19) R^5 is hydrogen,

(20) R^5 is hydroxy,

(21) R^5 is [(lower)alkoxy]carbonyl, or cyano,

(22) R^5 is [(C1-C4)alkoxy]carbonyl,

(23) R^5 is amino, [(lower)acyl]amino,

[(lower)alkoxy]carbonylamino, carbamoylamino, or [(lower)alkyl]sulfonylamino,

(24) R^5 is amino, [(C1-C4)acyl]amino, [(C1-C4)alkoxy]carbonylamino, carbamoylamino, or [(C1-C4)alkyl]sulfonylamino,

(25) R^5 is [(lower)acyl]oxy, or[(lower)alkyl]sulfonyloxy,

(26) R^5 is heteroaryl,

(27) X is "O", or "S",

(28) X is "O",

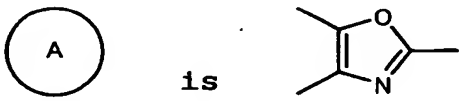
(29) X is "SO", or "SO_2",

(30) Y is "CH",

(31) Y is "N",

(32) n is 0,

(33) n is 1,

(34)  is ,

(35)  is ,

(36) substituent(s) (i) is(are) selected from the group consisting of (lower)alkoxy, hydroxy, aryl[(lower)alkyl]oxy, and [(lower)acyl]oxy,

(37) substituent(s) (i) is(are) selected from the group consisting of (C1-C4)alkoxy, hydroxy, aryl[(C1-C4)alkyl]oxy, and [(C1-C4)acyl]oxy,

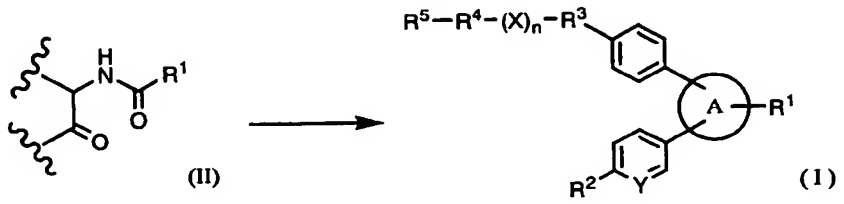
(38) substituent(s) (i) is(are) halogen,

(39) substituent(s) (ii) is(are) (lower)alkyl, which may be cyclized together,

(40) substituents (ii) are a (lower)alkyl, and a (lower)alkoxy.

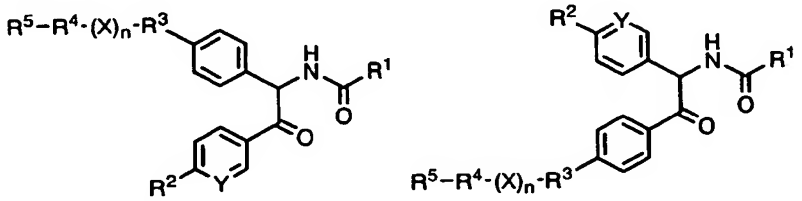
The compound of the formula (I) of the present invention can be prepared according to the following process A-1 to A-3.

[Process A-1]



(II) (I)

In the above formula, R^1 to R^5, A, X, Y and "n" represent the same meanings as defined above. And Compound (II) may have either of following structure.



Hereinafter, this condition is the same with Compound (III), (IV), (VI) and (VII).

Process A-1 is the process for preparing Compound (I) from Compound (II) by forming oxazole ring.

Compound (II) may be purchased if it is commercial, or synthesized according to Process B mentioned after or other general methods obvious to the person skilled in the organic chemistry from commercial compounds.

As this process, two methods are mainly employable, which are one using phosphorus oxychloride ($POCl_3$) as condensation agent (A-1(1)) and the other using triphenylphosphine (A-1(2)).

Process A-1(1) is generally carried out by adding phosphorus oxychloride to the solution of Compound (II).

The temperature at that time varies depending on the starting material, the solvent, etc., but it is usually room temperature. And after adding, the temperature is preferably raised to reflux.

The solvent employable in Process A-1(1) is not particularly limited so long as it is inactive in this reaction and resolve moderately Compound (II) and phosphorus oxychloride, and may preferably include liquid hydrocarbon such as benzene, toluene.

The reaction time after the adding varies depending on the starting material, the solvent, etc., but it is usually from 12hrs to 3days.

Process A-1(2) is generally carried out by adding the solution of triphenylphosphine, iodine and base (triethylamine, etc.) to the solution of Compound (II). The temperature at that time varies depending on the starting material, the solvent, etc., but it is usually room temperature.

The solvent employable in Process A-1(2) is not particularly limited so long as it is inactive in this reaction and can resolve substrates moderately, and may preferably include halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride.

The reaction time after the adding varies depending on the starting material, the solvent, etc., but it is usually from 12hrs to 3days.

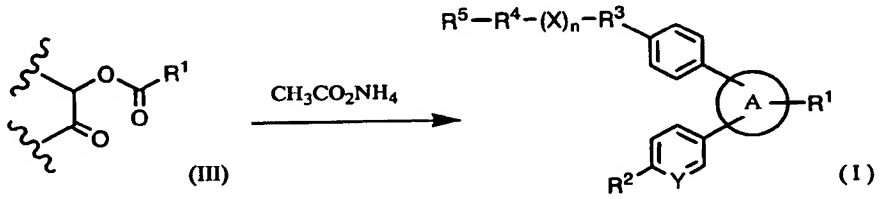
After the reaction, the mixture is partitioned between water and organic solvent insoluble with water such as ethyl acetate, $CHCl_3$, tc., and organic layer is separated. The organic layer is washed by water,

hydrochloric acid, saturated sodium bicarbonate solution, brine, etc., dried over anhydrous $MgSO_4$ or Na_2SO_4, and evaporated in vacuo. The target compound is purified by the conventional method such as silica gel column chromatography, etc..

Which to be selected A-1(1) or A-1(2) in this process is mainly dependent on the property of R^1 group. So, either method of which yield is higher may be employed.

Compound (I) can be also synthesized by following Process A-2.

[Process A-2]



(III) (I)

In the above formula, R^1 to R^5, A, X, Y and "n" represent the same meanings as defined above.

Process A-2 is the process for preparing Compound (I) from Compound (III) by forming oxazole ring besides Process A-1.

Compound (III) may be purchased if it is commercial, or synthesized according to Process C mentioned after or other general methods obvious to the person skilled in the organic chemistry from commercial compounds.

This process is generally carried out by adding ammonium acetate to the acetic acid solution of Compound (III). The temperature at that time varies depending on the starting material, the solvent, etc., but it is usually room temperature. And after adding, the temperature is

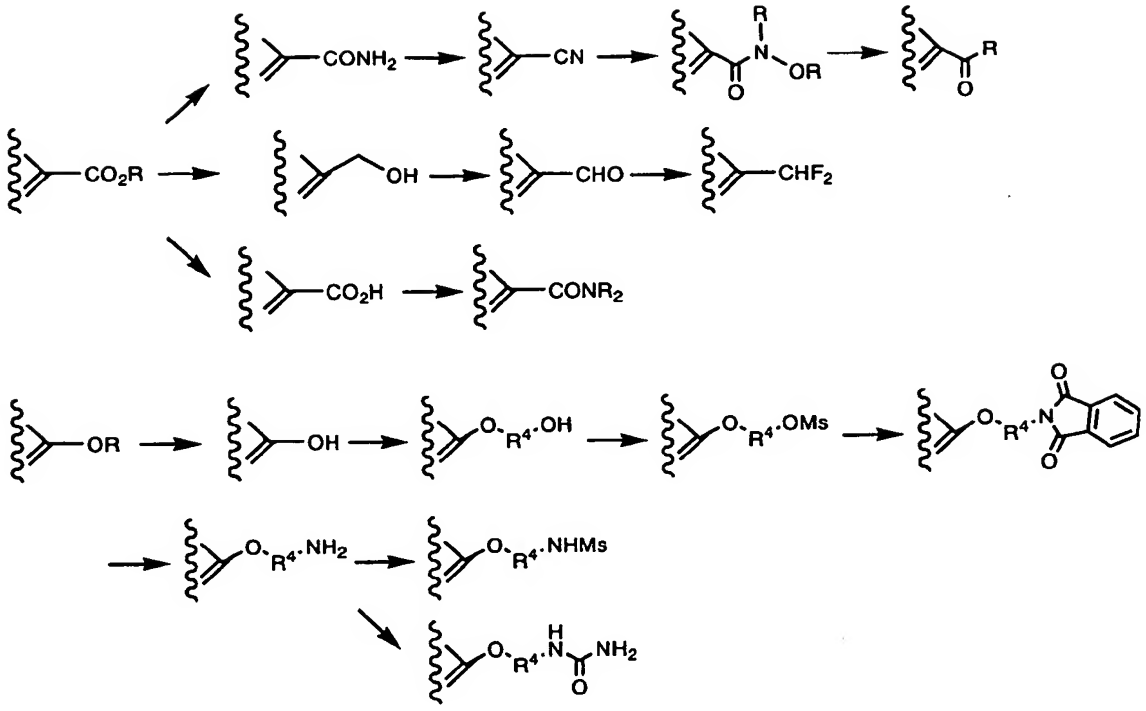
preferably raised to reflux.

The reaction time after the adding varies depending on the starting material, the solvent, tc., but it is usually from 30min to 12hrs, preferably from 1hr to 5hrs.

After the reaction, the solvent is removed in vacuo, and acetic acid is azeotropically removed with toluene, etc.. The residue is partitioned between water and organic solvent insoluble with water such as ethyl acetate, chloroform, etc., and organic layer is separated. The organic layer is washed by water, saturated sodium bicarbonate solution, brine, etc., dried over anhydrous $MgSO_4$ or Na_2SO_4, and evaporated in vacuo. The target compound is purified by the conventional method such as silica gel column chromatography, etc..

Compound (I) can be transformed the other Compound (I) by functional group trans formation, which is obvious to the person skilled in the organic chemistry. For example, first, Process A-1 or A-2 are carried out by using the compound which does not have reactive group as R^1 and the like, then, the R^1 and the like are transformed to reactive group. Some of such functional group trans formation reactions are illustrated as following.

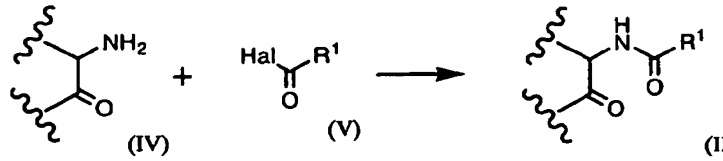
[Process A-3]



In the above formulae, R represents H, lower alkyl or aryl, which is not specified, and plural R may be same or different each other. "Ms" represents methanesulfonyl group. And R^4 represents the same meanings as defined above.

Compound (II), which is the starting compound of Process A-1, can be synthesized by following Process B.

[Process B]



(IV) (V) (II)

In the above formula, R^1 represents the same meanings as defined above. And "Hal" represents halogen atom, especially, chlorine or bromine atom.

Process B is the process for preparing the Compound

(II) by condensing Compound (IV) and (V).

Compound (IV) and (V) may be purchased if it is commercial, or synthesized according to general methods obvious to the person skilled in the organic chemistry from commercial compounds. But, in advance, Compound (V) can be synthesized from corresponding acid and pivaloyl chloride or oxallyl chloride, or the like, in one-pot. And corresponding acid anhydride may be also used as Compound (V).

This process is generally carried out by adding Compound (V) to the solution of Compound (IV). To accelerate the reaction, base such as pyridine may be added. The temperature at that time varies depending on the starting material, the solvent, etc., but it is usually 0 ℃ to room temperature. And after adding, the temperature may be raised to reflux.

The solvent employable in Process B is not particularly limited so long as it is inactive in this reaction and resolve moderately substrates, and may include preferably halogenated hydrocarbon such as dichloromethane, chloroform; liquid hydrocarbon such as benzene, toluene; ethers such as diisopropyl ether, tatrahydrofuran, dioxane.

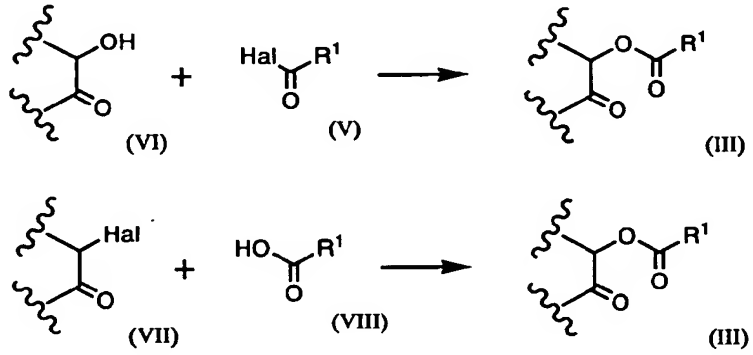
The reaction time after the adding varies depending on the starting material, the solvent, etc., but it is usually from 1hr to 3days.

After the reaction, the mixture is partitioned between water and organic solvent insoluble with water such as ethyl acetate, chloroform, etc., and organic layer is separated. The organic layer is washed by wat r,

hydrochloric acid, saturated sodium bicarbonate solution, brine, etc., dried over anhydrous $MgSO_4$ or Na_2SO_4, and evaporated in vacuo. The target compound is purified by the conventional method such as silica gel column chromatography, etc.. However, the target compound may be used in next step (Process A-1) without purification.

Compound (III), which is the starting compound of Process A-2, can be synthesized by following Process C.

[Process C]



In the above formulae, R^1 and "Hal" represent the same meanings as defined above.

Process C is the process for preparing the Compound (III) in the presence of base.

Compound (V) to (VIII) may be purchased if it is commercial, or synthesized according to general methods obvious to the person skilled in the organic chemistry from commercial compounds, for their structure are comparatively simple.

The above two processes may be generally carried out by almost same condition, that is, by mixing base and Compound (V) and (VI) or Compound (VII) and (VIII) in solvent. The temperature at that time varies depending

on the starting material, the solvent, etc., but it is usually room temperature.

The solvent employable in Process C is not particularly limited so long as it is inactive in this reaction and resolve moderately substrates, and may include preferably halogenated hydrocarbon such as dichloromethane, chloroform; ketone such as acetone, 2-butanone.

The base employable in this process for making basic condition is not particularly limited so long as it accelerates this reaction and may include alkali metal carbonates such as lithium carbonate, sodium carbonate, potassium carbonate; alkaline earth metal carbonates such as magnesium carbonate, calcium carbonate; cesium carbonate; pyridine.

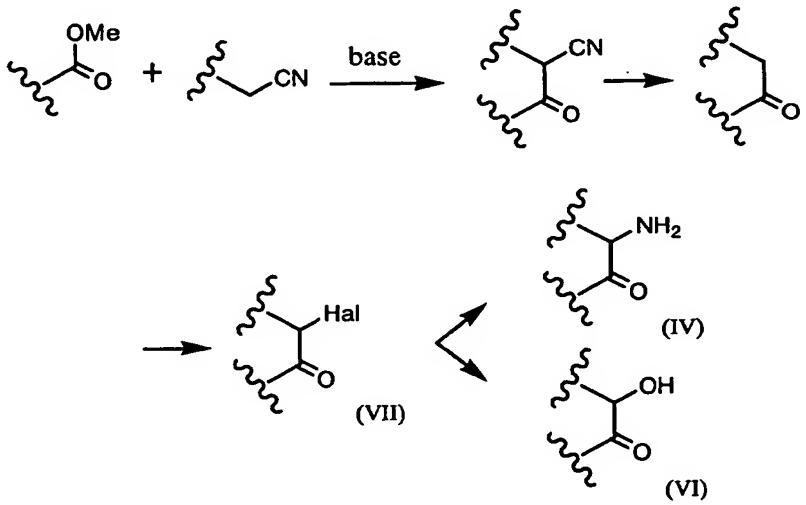
The reaction time varies depending on the starting material, the solvent, etc., but it is usually from 12hrs to 2days.

After the reaction, the mixture is partitioned between water and organic solvent insoluble with water such as ethyl acetate, chloroform, etc., and organic layer is separated. The organic layer is washed by water, hydrochloric acid, saturated sodium bicarbonate solution, brine, etc., dried over anhydrous $MgSO_4$ or Na_2SO_4, and evaporated in vacuo. The target compound is purified by the conventional method such as silica gel column chromatography, etc.. However, the target compound may be used in next step (Process A-2) without purification.

Compound (IV), (VI) and (VII) have comparably simple

structure. So, these compounds can be synthesized according to general methods obvious to the person skilled in the organic chemistry from commercial compounds. For example, these compounds can be synthesized by referring following Process D.

[Process D]



Above Processes A to D, all starting materials and product compounds may be salts. The compounds of above processes can be converted to salt according to a conventional method.

And above Processes A to D, compounds, which have reactive group, may be protected timely at the group, and be deprotected timely. In these reactions (protecting or deprotecting steps), concerning the kind of protective group and the condition of the reaction, 「PROTECTIVE GROUPS IN ORGANIC SYNTHESIS Second Edition」 T.W.Green and P.G.M.Wuts, John Wiley & Sons, INC. may be referred.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present

invention can be used in a form of pharmaceutical preparation containing said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, cream, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

For therapeutic purpose, the analgesic agent of the present invention can be used in a form of pharmaceutical preparation suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like.

Particularly, the analgesic agent of this invention is useful for treating or preventing acute or chronic pains associated with acute or chronic inflammations in human beings or animals by using administered systemically or topically.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100

mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

THE BEST MODE FOR CARRYING OUT THE INVENTION

The patents, patent applications and publications cited herein are incorporated by reference.

The following Examples are given only for the purpose of illustrating the present invention in more detail.

Example 1-1

Ethyl {[1,2-bis(4-methoxyphenyl)-2-oxoethyl]amino}(oxo)acetate

To a suspension of 2-amino-1,2-bis(4-methoxyphenyl)ethanone hydrochloride (1.0g, 3.25mmol) in benzene (10mL) was added ethyl chlorooxoacetate (532mg, 3.90mmol) at room temperature and the mixture was heated to reflux with stirring for 2days.

After cooling, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated in vacuo to give the title compound (1.25g, 103.6%) as an oil.

1H-NMR (300MHz, $CDCl_3$) : δ 1.37(3H, t, J=7.5Hz), 3.75(3H, s), 3.83(3H, s), 4.34(2H, q, J=7.5Hz), 6.42(1H, d, J=7.5Hz), 6.83(2H, d, J=8Hz), 6.87(2H, d, J=8Hz), 7.34(2H, d, J=8Hz), 7.95(2H, d, J=8Hz), 8.49(1H, d, J=7.5Hz).
MS (ES+) : 372.14.

Example 1-2

Ethyl 4,5-bis(4-methoxyphenyl)-1,3-oxazole-2-carboxylate

To a solution of ethyl {[1,2-bis(4-methoxyphenyl)-2-oxoethyl]amino}(oxo)acetate obtained by Example 1-1 (1.25g, 3.37mmol) in benzene (15mL) was added phosphorus oxychloride (1.55g, 10.1mmol) at room temperature and the mixture was heated to reflux with stirring for 18hrs.

After cooling, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=4:1) to give the title compound (909mg, 76.4%) as a pale yellow powder.

MP : 95-97℃.

1H-NMR (300 MHz, $CDCl_3$) : δ 1.46(3H, t, J=7.5Hz), 3.84(3H, s), 3.85(3H, s), 4.51(2H, q, J=7.5Hz), 6.91(4H, d-like, J=8Hz), 7.58-7.62(4H, m).

MS (ES+) : 354.10.

Example 2

4,5-Bis(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

A mixture of ethyl 4,5-bis(4-methoxyphenyl)-1,3-oxazole-2-carboxylate obtained by Example 1-2 (400mg, 1.13mmol) and sodium methoxide (183mg, 3.40mmol) in fo

rmamide (4mL) was stirred at 100℃ for 2hrs.

After cooling to room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer washed with water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with isopropyl ether to give the title compound (264mg, 71.9%) as a pale yellow powder.

MP : 133-135℃.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.79(3H, s), 3.81(3H, s), 7.00(2H, d, J=8 Hz), 7.05(2H, d, J=8 Hz), 7.52(2H, d, J=8 Hz), 7.55(2H, d, J=8 Hz), 7.93(1H, br-s), 8.30(1H, br-s).

MS (ES+) : 325.10.

Example 3

4,5-Bis(4-methoxyphenyl)-1,3-oxazole-2-carbonitrile

A mixture of 4,5-bis(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 2 (239mg, 0.737mmol) and phosphorus oxychloride (339mg, 2.21mmol) in N,N-dimethylformamide (2mL) was stirred at room temperature for 1hr.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was crystallized from a mixture of ethyl acetate and n-h xane to give the title compound (175mg, 77.5%) as pale yellow crystals.

MP : 110-112℃.

1H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 3.86(3H, s), 6.94(4H, d, J=9 Hz), 7.55(4H, d, J=9 Hz).

IR (KBr) : 2240 cm^{-1}.

Example 4

N-Methoxy-4,5-bis(4-methoxyphenyl)-N-methyl-1,3-oxazole-2-carboxamide

To a solution of N,O-dimethylhydroxyamine hydrochloride (414mg, 4.24mmol) in tetrahydrofuran (8mL) was added triethylaluminum (15% solution in hexane) dropwise at 0℃ under nitrogen and the mixture was stirred at room temperature for 1hr. A solution of ethyl 4,5-bis(4-methoxyphenyl)-1,3-oxazole-2-carboxylate obtained by Example 1-2 (500mg, 1.41mmol) in tetrahydrofuran (10mL) was added dropwise to the mixture at 0℃ and the reaction mixture was stirred at 0℃ for 18hrs.

The mixture was poured into 1mol/L hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=4:1) to give the title compound (475mg, 91.1%) as an amorphous powder.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.53(3H, br peak), 3.85(6H, s), 3.95(3H, s), 6.86-6.95(4H, m), 7.60(4H, s).

MS (ES+) : 369.53(M+H), 737.39(2M+H), 759.77(2M+Na).

Example 5

1-[4,5-Bis(4-methoxyphenyl)-1,3-oxazol-2-yl]ethanone

To a solution of N-methoxy-4,5-bis(4-methoxypheny l)-N-methyl-1,3-oxazole-2-carboxamide obtained by Exa mple 4 (120mg, 0.326mmol) in tetrahydrofuran (3mL) was added 1N solution of methylmagunesium bromide in tetr ahydrofuran (1.0mL, 0.95mmol) dropwise at 0℃ under ni trogen and the mixture was stirred at the same tempera ture for 2hrs.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was crystallized from a mixture of ethyl acetate and hexane to give the title compound (63mg, 59.8%) as pale yellow crystals.

MP : 139-140℃.

1H-NMR (300MHz, $CDCl_3$) : δ 2.72(3H, s), 3.85(3H, s), 3.86(3H, s), 6.90(2H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.58(2H, d, J=8Hz), 7.63(2H, d, J=8Hz).

MS (ES+) : 324.40(M+H), 647.68(2M+H).

Example 6

[4,5-Bis(4-methoxyphenyl)-1,3-oxazol-2-yl](phenyl)met hanone

The title compound (193mg, 61.5%) as yellow crysts was prepared from N-methoxy-4,5-bis(4-methoxyphenyl)-N-methyl-1,3-oxazole-2-carboxamide obtained by Example 4 (300mg, 0.814mmol) and 3N solution of phenylmagunesium bromide in diethyl ether (0.82mL, 2.46mmol) in a similar manner to that of Example 5.

MP : 164-166℃.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.86(3H, s), 3.87(3H, s), 6.93(2H, d, J=8Hz), 6.96(2H, d, J=8Hz), 7.49-7.57(2H, m), 7.60-7.71(5H, m), 7.53-7.59(2H, m).

MS (ES+) : 386.30.

Example 7-1

2-(4-Methoxyphenyl)-3-(6-methoxy-3-pyridinyl)-3-oxopropanenitrile

To a stirred suspension of potassium tert-butoxide (3.69g, 32.9mmol) in tert-butanol (40mL) was added methyl 6-methoxynicotinate (5.0g, 29.9mmol) followed by dropwise addition of (4-methoxyphenyl)acetonitrile (4.4g, 29.9mmol) in tert-butanol (10mL) at room temperature. The resulting mixture was heated at 120℃ for 1.5hrs.

The mixture was allowed to cool and water was added to the mixture (160mL). The mixture was extracted with ether (100mL) and the aqueous phase was separated. The aqueous layer was neutralized with hydrogen chloride (37%) and then extracted with ethyl acetate (100mL). The

organic layer was separated, washed with water (100mL) and brine (100mL) and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to give the title compound (6.49g, 77%) as a brown viscous oil.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.80(3H, s), 3.99(3H, s), 5.44(1H, s), 6.78(1H, d, J=8.8Hz), 6.92(2H, d, J=8.8Hz), 7.35(2H, d, J=8.8Hz), 8.12(1H, dd, J=8.8,2.6Hz), 8.78(1H, d, J=2.6Hz).

Example 7-2

1-(6-Hydroxy-3-pyridinyl)-2-(4-methoxyphenyl)ethanone

To a stirred solution of 2-(4-methoxyphenyl)-3-(6-methoxy-3-pyridinyl)-3-oxopropanenitrile obtained by Example 7-1 (4.19g, 14.8mmol) in 1,4-dioxane (20mL) was added hydrogen chloride (37%, 40mL) and the resulting mixture was heated at 80℃ for 20hrs.

The mixture was allowed to cool and the solvent was removed in vacuo. The residual solid was suspended in water (50mL) and the suspension was neutralized with saturated sodium bicarbonate solution. The precipitate was filtered and washed with water to afford the title compound (3.17g, 88%) as a brown solid.

MP : 177-181℃.

1H-NMR (300 MHz, DMSO-d6) : δ 3.72(3H, s), 4.10(2H, s), 6.37(1H, d, J=9.6Hz), 6.87(2H, d, J=8.8Hz), 7.15(2H, d, J=8.8Hz), 7.87(1H, dd, J=9.6,2.6Hz), 8.35(1H, d, J=2.6Hz).

Exampl 7-3

1-(6-Chloro-3-pyridinyl)-2-(4-methoxyphenyl)ethanone

A suspension of 1-(6-hydroxy-3-pyridinyl)-2-(4-methoxyphenyl)ethanone obtained by Example 7-2 (3.80g, 15.6mmol) in phosphorous oxychloride (12mL) was heated at 80℃ for 1hr.

The mixture was concentrated in vacuo and the residue was poured into ice-water (40mL). The mixture was neutralized with saturated sodium bicarbonate solution and stirred in ice bath for 1hr. The precipitate was filtered and washed with water to give the title compound (3.77g, 92%) as a pale brown solid.

MP : 77-81℃.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.79(3H, s), 4.21(2H, s), 6.87(2H, d, J=8.8Hz), 7.16(2H, d, J=8.8Hz), 7.42(1H, d, J=8.4Hz), 8.20(1H, dd, J=8.8,2.6Hz), 8.98(1H, d, J=2.6Hz).

MS (ES+) : 262.00(M+1).

Example 7-4

2-(4-Methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone

To a stirred suspension of 1-(6-chloro-3-pyridinyl)-2-(4-methoxyphenyl)ethanone obtained by Example 7-3 (3.66g, 14mmol) in methanol (40mL) was added 5.19M solution of sodium methoxide in methanol (3.0mL, 15.4mmol) at room temperature and the resulting

mixture was refluxed for 1.5hrs. Additional 5.19M solution of sodium methoxide in methanol (1.48mL, 7.7mmol) was added and the mixture was refluxed for 1.5hrs. The mixture was allowed to cool, and to this was added methanol (10mL) and neutralized with hydrogen chloride (37%). To the suspension was added water (10mL) and the mixture was stirred in ice bath for 1hr. The precipitate was filtered and washed with water (10mL) three times to afford the title compound (2.96g, 82%) as an off-white solid.

MP : 101-102℃.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.78(3H, s), 3.99(3H, s), 4.16(2H, s), 6.77(1H, d, J=8.8Hz), 6.86(2H, d, J=8.4Hz), 7.18(2H, d, J=8.4Hz), 8.16(1H, dd, J=8.8,2.6Hz), 8.85(1H, d, J=2.6Hz).

MS (ES+) : 258.09(M+1).

Example 7-5

2-Azido-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl) ethanone

To a solution of 2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone obtained by Example 7-4 (3.0g, 11.7mmol) in dichloromethane (30mL) were added pyridinium tribromide (4.1g, 12.8mmol) and hydrogen bromide (33% solution in acetic acid, 3mL) at room temperature under nitrogen and the mixture was stirred at the same temperature for 40min.

The reaction mixtur was evaporated in vacuo and ac tic acid was azeotropically removed with toluene. The

residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated in vacuo.

The residue was dissolved in N,N-dimethylformamide (15mL). To the solution was added sodium azide (758mg, 11.7mmol) at 0℃ and the mixture was stirred at room temperature for 1hr.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=4:1) to give the title compound (1.5g, 43.1%) as an oil.

1H-NMR (300 MHz, DMSO-d6) : δ 3.77(3H, s), 3.92(3H, s), 5.55(1H, s), 6.70(1H, d, J=8Hz), 6.90(2H, d, J=8Hz), 7.20-7.40(3H, m), 8.06(1H, dd, J=8,2Hz) , 8.64(1H, d, J=2Hz).
MS (ES+) : 299.06.

Example 7-6
2-Amino-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl) ethanone hydrochloride

A mixture of 2-azido-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone obtained by Example 7-5 (1.

5g, 5.03mmol), hydrochloric acid (37%, 0.42mL) and 10% palladium on carbon (300mg) in methanol (40mL) was stirred at room temperature under hydrogen for 30min.

The reaction mixture was filtered through Celite and evaporated in vacuo. The residue was triturated with diethyl ether to give the title compound (1.46g, 94.0%) as a pale yellow powder.

1H-NMR (300 MHz, DMSO-d6) : δ 3.73(3H, s), 3.91(3H, s), 6.21-6.34(1H, m), 6.92(1H, d, J=8Hz), 6.99(2H, d, J=8Hz), 7.49(2H, d, J=8Hz), 8.25(1H, dd, J=8,2Hz), 8.82-8.99(3H, m).

Example 7-7

2-Methoxy-N-[1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl]acetamide

To a solution of 2-amino-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone hydrochloride obtained by Example 7-6 (150mg, 0.489mmol) and pyridine (115mg, 1.46mmol) in dichloromethane (3mL) was added methoxyacetyl chloride (74.6mg, 0.632mmol) under nitrogen at room temperature and the mixture was stirred at the same temperature for 2hrs.

The mixture was pored into 1mol/L hydrochloric acid and extracted with chloroform. The organic layer was washed with 1mol/L hydrochloric acid and water, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (toluene : ethyl acetate=3:1) to give the title compound

(100mg, 59.6%) as an oil.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.44(3H, s), 3.76(3H, s), 3.92(2H, s), 3.96(3H, s), 6.43(1H, d, J=8Hz), 6.74(1H, d, J=8Hz), 6.85(2H, d, J=8Hz), 7.31(2H, d, J=8Hz), 7.82(1H, d, J=8Hz), 8.12(1H, dd, J=8,2Hz), 8.80 (1H, d, J=2Hz).

Example 7-8

2-Methoxy-5-[2-(methoxymethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]pyridine

The title compound (32mg, 33.8%) was prepared as an amorphous from 2-methoxy-N-[1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl]acetamide obtained by Example 7-7 (100mg, 0.29mmol) in a similar manner to that of Example 1-2.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.52(3H, s), 3.84(3H, s), 3.97(3H, s), 4.60(2H, s), 6.75(1H, d, J=8Hz), 6.91(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.76(1H, dd, J=8,2Hz), 8.41(1H, d, J=2Hz).
MS (ES+) : 327.07.

Example 8-1

2-{[1-(4-Methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl]amino}-2-oxoethyl acetate

The title compound (673mg, 38%) was prepared from 2-amino-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl) ethanone hydrochloride obtained by Example 7-6 (1.47g,

4.76mmol) and acetoxyacetyl chloride (731mg, 6.19mmol) in a similar manner to that of Example 7-7.

1H-NMR (300 MHz, $CDCl_3$) : δ 2.22(3H, s), 3.76(3H, s), 3.96(3H, s), 4.54(1H, d, J=15Hz), 4.62(1H, d, J=15Hz), 6.40(1H, d, J=8Hz), 6.74(1H, d, J=8Hz), 6.85(2H, d, J=8Hz), 7.31(2H, d, J=8Hz), 7.59(1H, d, J=8Hz), 8.11(1H, dd, J=8,2Hz), 8.80(1H, d, J=2Hz).
MS (ES+) : 373.06.

Example 8-2

[4-(4-Methoxyphenyl)-5-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methanol

To a solution of 2-{[1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl]amino}-2-oxoethyl acetate obtained by Example 8-1 (670mg, 1.8mmol) in toluene (12mL) was added phosphorus oxychloride (828mg, 5.4mmol) at room temperature and the mixture was heated to reflux with stirring for 15hrs.

After cooling, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated in vacuo.

The residue was dissolved in methanol. To a solution was added potassium carbonate (49.7mg) at room temperature and the mixture was stirred at the same temperature for 1hr.

The reaction mixtur was evaporated in vacuo and the

residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=1:1) to give the title compound (26mg, 4.6%) as an amorphous solid.

1H NMR (300MHz, $CDCl_3$) : δ 2.58(1H, t, J=7H), 3.84(3H, s), 3.97(3H, s), 4.81(2H, d, J=7Hz), 6.75(1H, d, J=8Hz), 6.91(2H, d, J=8Hz), 7.53(2H, d, J=8Hz), 7.74(1H, dd, J=8.2Hz), 8.40(1H, d, J=2Hz).
MS (ES+) : 313.10.

Example 9-1
1-[4-(Benzyloxy)phenyl]-2-bromo-2-(4-methoxyphenyl)ethanone

The title compound (20.65g, 99.9%) was prepared as an oil from 1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)ethanone (16.7g, 50.2mmol) in a similar manner to that of Example 78-3 described later.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.80(3H, s), 5.12(2H, s), 6.36(1H, s), 6.89(2H, d, J=8Hz), 6.99(2H, d, J=8Hz), 7.31-7.50(7H, m), 7.96(2H, d, J=8 Hz).

Example 9-2
2-[2-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoe

thyl]-1H-isoindole-1,3(2H)-dione

To a solution of 1-[4-(benzyloxy)ph nyl]-2-bromo-2-(4-methoxyphenyl)ethanone obtained by Example 9-1 (20.65g, 50.2mmol) in N,N-dimethylformamide (200mL) was added potassium phthalimide (9.3g, 50.2mmol) at 0℃ and the mixture was stirred at the same temperature for 2hrs.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was triturated with ethanol to give the title compound (20.47g, 85.4%) as a powder.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.77(3H, s), 5.07(2H, s), 6.70(1H, s), 6.85(2H, d, J=8Hz), 6.91(2H, d, J=8Hz), 7.30-7.47(7H, m), 7.65-7.73(2H, m), 7.78-7.88(4H, m).

Example 9-3

2-Amino-1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)ethanone hydrochloride

To a suspension of 2-[2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-1H-isoindole-1,3(2H)-dione obtained by Example 9-2 (20.47g, 42.9mmol) in ethanol (200mL) was added hydrazine monohydrate (8.58g, 171mmol) at room temperatur and th mixture was heated to r flux with

stirring for 30min.

After cooling, hydrochloric acid (37%, 24mL) was added to the mixture and the precipitate was filtered off. The filtrate was concentrated in vacuo and the residue was triturated with ethyl acetate to give the title compound (10.62g, 64.5%) as a powder.

1H-NMR (300 MHz, DMSO-d6) : δ 3.72(3H, s), 5.18(2H, s), 6.24(1H, br peak), 6.96(2H, d, J=8 Hz), 7.10(2H, d, J=8Hz), 7.24-7.50(7H, m), 8.00(2H, d, J=8Hz), 8.77(2H, br peak).
MS (ES+) : 348.16.

Example 9-4

N-[2-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-2,2-difluoroacetamide

To a mixture of difluoroacetic acid (981mg, 10.2mmol) and triethylamine (1.77g, 17.5mmol) in tetrahydrofuran (50mL) was added pivaloyl chloride (1.23g, 10.2mmol) dropwise at 0℃ under nitrogen and the mixture was stirred at the same temperature for 1hr. 2-Amino-1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)ethanone hydrochloride obtained by Example 9-3 (2.8g, 7.29mmol) was added portionwise to the mixture at 0℃ and the reaction mixture was stirred at the same temperature for 2hrs.

The reaction mixture was evaporated in vacuo and partitioned between water and ethyl acetate. The organic layer was separated, washed with water, saturated sodium bicarbonate solution and brine, successively, dried over

magnesium sulfate. After evaporation of solvent, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=3:1) to give th title compound (2.0g, 64.5%) as an oil.

1H NMR (300MHz, $CDCl_3$) : δ 3.76(3H, s), 5.09(2H, s), 5.89(1H, t, J=53Hz), 6.40(1H,br-s), 6.84(2H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.26-7.43(7H, m), 7.84-7.98(3H, m).

Example 9-5

5-[4-(Benzyloxy)phenyl]-2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazole

To a mixture of triphenylphosphine (6.88g, 26.2mmol), iodine (6.66g, 26.2mmol) and triethylamine (5.31g, 52.5mmol) in dichloromethane (100mL) were added a solution of N-[2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-2,2-difluoroacetamide obtained by Example 9-4 (5.58g, 13.1mmol) in dichloromethane (10mL) at room temperature under nitrogen and the mixture was stirred at the same temperature for 2days.

The reaction mixture was evaporated in vacuo and partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, successively, dried over magnesium sulfate. After evaporation of solvent, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=3:1) and triturated with p troleum ether to give the title compound (3.43g, 64.2%) as a powder.

1H-NMR (300MHz, $CDCl_3$) : δ 3.84(3H, s), 5.10(2H, s), 6.70(H, t, J=53Hz), 6.91(2H, d, J=8Hz), 6.98(2H, d, J=8Hz), 7.29-7.46(5H, m), 7.50-7.60(4H, m).

Example 10

4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol

The title compound (2.75g, 103.2%) was prepared as a powder from 5-[4-(benzyloxy)phenyl]-2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazole obtained by Example 9-5 (3.42g, 8.39mmol) in a similar manner to that of Example 65 described later.

1H-NMR (300MHz, $CDCl_3$) : δ 3.84(3H, s), 5.27(1H, s), 6.70(1H, t, J=53Hz), 6.85(2H, d, J=8Hz), 6.92(2H, d, J=8Hz), 7.51(2H, d, J=8Hz), 7.56(2H, d, J=8Hz)
MS (ES-) : 316.19.

Example 11

Ethyl {4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}acetate

To a suspension of sodium hydride (60% in oil, 410 mg, 10.2mmol) in N,N-dimethylformamide (5mL) was added a solution of 4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol obtained by Example 10 (2.5g, 9.85mmol) in N,N-dimethylformamide (20mL) dropwise at 0℃ under nitrogen and the mixture was stirr d at

the same temperature for 1hr. Then ethyl bromoacetate (1.64g, 9.85mmol) was added and stirred at the same temperature for 3hrs.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was crystalized from a mixture of water and ethanol to give the title compound (2.66g, 83.7%) as crystals.

1H-NMR (300MHz, $CDCl_3$) : δ 1.31(3H, t, J=7.5Hz), 3.85(3H, s), 4.28(2H, q, J=7.5Hz), 4.66(2H, s), 6.69(1H, t, J=53Hz), 6.88-6.95(4H, m), 7.54(2H, d, J=8Hz), 7.58(2H, d, J=8Hz)
MS (ES+) : 404.13.

Example 12

2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanol

To a solution of ethyl {4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}acetate obtained by Example 11 (4.3g, 10.7mmol) in a mixture of diethyl ether (40mL) and tetrahydrofuran (10mL) was added lithium aluminum hydride (405mg, 10.7mmol) portionwise at 0℃ under nitrogen and the mixture was stirred at the same temperature for 3hrs.

To the reaction mixture was added water dropwise at 0℃. The precipitate was removed by vacuum filtration and the filtrate was evaporated in vacuo. The residue

was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=2:1) and crystallized from a mixture of ethyl acetate and n-hexane to give the title compound (3.1g, 80.5%) as white crystals.

MP : 114-116℃.

1H-NMR (300MHz, $CDCl_3$) : δ 2.02(1H, t, J=7Hz), 3.85(3H, s), 3.98(2H, td, J=5,7Hz), 4.12(2H, t, J=5Hz), 6.70(1H, t, J=52Hz), 6.91(2H, d, J=8Hz),6.94(2H, d, J=8Hz), 7.52-7.60 (4H, m).

MS (ES+) : 362.13.

Example 13

3-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}-1-propanol

To a solution of 4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol obtained by Example 10 (40mg, 0.126mmol) in N,N-dimethylformamide (1mL) were added 3-bromo-1-propanol (26.3mg, 0.189mmol) and potassium carbonate (52.3mg, 0.378mmol) at room temperature and the mixture was stirred at the same temperature for 18hrs.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was

washed with 1mol/L hydrochloric acid , water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=1:1) to give the title compound (25mg, 52.8%) as an oil.

1H-NMR (300 MHz, $CDCl_3$) : δ 1.64(1H, br peak), 2.01-2.14(2H, m), 3.84(3H, s), 3.88(2H, t, J=5Hz), 4.16(2H, t, J=5Hz), 6.69(1H, t, J=53Hz), 6.88-6.95(4H, m), 7.50-7.60(4H, m).
MS (ES+) : 376.07.

Example 14

{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}acetonitrile

The title compound (241mg, 71.5%) was prepared as a powder from 4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol (300mg, 0.946mmol) and iodoacetonitrile (316mg, 1.89mmol) in a similar manner to that of Example 13.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.85(3H, s), 4.82(2H, s), 6.71(1H, t, J=53Hz), 6.94(2H, d, J=8Hz), 7.00(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.64(2H, d, J=8 Hz).

Example 15

N-(2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)ac tamide

To a solution of {4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}acetonitrile obtained by Example 14 (97mg, 0.272mmol) in tetrahydrofuran (2mL) was added lithium aluminum hydride (12.4mg, 0.327mmol) at 0℃ under nitrogen and the mixture was stirred at the same temperature for 3hrs. To the reaction mixture was added water dropwise at 0℃.

The precipitate was removed by vacuum filtration and the filtrate was evaporated in vacuo. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo.

The residue was dissolved in dichloromethane (2mL). To the solution were added pyridine (64.6mg, 0.817mmol) and acetyl chloride (25.6mg, , 0.327mmol) at 0℃ and the mixture was stirred at the same temperature for 2hrs.

The reaction mixture was evaporated in vacuo and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (ethyl acetate : chloroform : n-hexane=12:7:1) to give the title compound (28mg, 25.6%) as a powder.

1H-NMR (300MHz, $CDCl_3$) : δ 2.03(3H, s), 3.68(2H, q, J=5Hz), 3.85(3H, s), 4.08(2H, t, J=5Hz), 5.93(1H, br peak),

6.70(1H, t, J=53Hz), 6.86-6.96(4H, m), 7.51-7.60(4H, m). MS (ES+) : 403.10.

Example 16

tert-Butyl 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylcarbamate

To a solution of {4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}acetonitrile obtained by Example 14 (245mg, 0.688mmol) in tetrahydrofuran (2mL) was added lithium aluminum hydride (31.3mg, 0.825mmol) at 0℃ under nitrogen and the mixture was stirred at the same temperature for 3hrs.

To the reaction mixture was added water dropwise at 0℃. The precipitate was removed by vacuum filtration and the filtrate was evaporated in vacuo. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo.

The residue was dissolved in dichloromethane (2mL). To a solution were added triethylamine (83.5mg, 0.115mmol) and di-tert-butyl dicarbonate (180mg, 0.115mmol) 0℃ and the mixture was stirred at the same temperature for 2hrs.

The reaction mixture was evaporated in vacuo and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (ethyl acetate :

n-hexane=1:1) to give the title compound (94mg, 29.7%) as an oil.

1H-NMR (300 MHz, $CDCl_3$) : δ 1.46(9H, s), 3.56(2H, q, J=5Hz), 3.85(3H, s), 4.06(2H, t, J=5Hz), 4.99(1H, br peak), 6.70(1H, t, J=53Hz), 6.88-6.95(4H, m), 7.51-7.59(4H, m).
MS (ES+) : 461.15.

Example 17

2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanamine hydrochloride

4N Hydrogen chloride solution in ethyl acetate (0.5mL) was added to a solution of 1-tert-butyl 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylcarbamate obtained by Example 16 (92mg, 0.2mmol) in ethyl acetate (1mL) at room temperature. The mixture was stirred at the same temperature for 3hrs.

After evaporation of solvent, the residue was triturated with ether to give the title compound (52mg, 65.6%) as an amorphous powder.

1H-NMR (300 MHz, DMSO-d6) : δ 3.24(2H, br pesk), 3.79(3H, s), 4.23(2H, t, J=5Hz), 7.00(2H, d, J=8Hz), 7.10(2H, d, J=8Hz), 7.31(1H, t, J=53Hz), 7.50(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 8.09(3H, br peak).
MS (ES+) : 361.13.

Example 18

N-(2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-o

xazol-5-yl]phenoxy}ethyl)urea

To a solution of 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanamine (136mg, 0.377mmol) in dichloromethane (3mL) was added trimethylsilyl isocyanate (87mg, 0.755mmol) at room temperature and the mixture was stirred at the same temperature for 24hrs.

The reaction mixture was poured into water and extracted with chloroform. The organic layer washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (chloroform : methanol=10:1) to give the title compound (95mg, 62.4%) as an amorphous powder.

MP : 146-149℃.

1H-NMR (300 MHz, DMSO-d6) : δ 3.25-3.40(2H, m), 3.80(3H, s), 4.00(2H, t, J=7Hz), 5.54(2H, s), 6.17(1H, t, J=7Hz), 7.00(2H, d, J=8Hz), 7.06(2H, d, J=8Hz), 7.29(1H, t, J=53Hz), 7.47-7.55(4H, m).

Example 19-1

Ethyl {[2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]amino}(oxo)acetate

The title compound (1.9g, 88.1%) was prepared as an oil from 2-amino-1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)ethanon hydrochloride (1.85g, 4.82mmol) an

d ethyl chlorooxoacetate (888mg, 6.51mmol) in a simila r manner to that of Example 1-1.

1H-NMR (300 MHz, $CDCl_3$) : δ 1.37(3H, t, J=7.5Hz), 3.75(3H, s), 4.34(2H, q, J=7.5Hz), 5.08(2H, s), 6.42(1H, d, J=7.5Hz), 6.82(2H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.29-7.45(7H, m), 7.94(2H, d, J=8Hz), 8.48(1H, d, J=7.5Hz).
MS (ES+) : 448.14.

Example 19-2
Ethyl 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3 -oxazole-2-carboxylate

The title compound (1.06g, 58.3%) was prepared as an oil from ethyl {[2-[4-(benzyloxy)phenyl]-1-(4-met hoxyphenyl)-2-oxoethyl]amino}(oxo)acetate obtained by Example 19-1 (1.9g, 4.25mmol) in a similar manner to that of Example 1-2.

1H-NMR (300 MHz, $CDCl_3$) : δ 1.45(3H, t, J=7.5Hz), 3.84(3H, s), 4.50(2H, q, J=7.5Hz), 5.10(2H, s), 6.91(2H, d, J=8Hz), 6.98(2H, d, J=8Hz), 7.30-7.46(5H, m), 7.55-7.65(4H, m).
MS (ES+) : 430.14.

Example 20
5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazo le-2-carboxamide

The title compound (980mg, 99.2%) was prepared as

a powder from ethyl 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxylate obtained by Example 19-2 (1.06g, 2.47mmol) in a similar manner to that of Example 2.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.85(3H, s), 5.09(2H, s), 5.76(1H, br peak), 6.90-7.04(5H, m), 7.30-7.46(5H, m), 7.56(2H, d, J=8Hz), 7.61(2H, d, J=8Hz).
MS (ES+) : 401.12.

Example 21
5-(4-Hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

The title compound (298mg, 91.6%) was prepared as a powder from 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 20 (420mg, 1.05mmol) in a similar manner to that of Example 65 described later.

1H-NMR (300 MHz, DMSO-d6) : δ 3.80(3H, s), 6.84(2H, d, J=8Hz), 7.00(2H, d, J=8Hz), 7.43(2H, d, J=8Hz), 7.53(2H, d, J=8Hz), 7.90(1H, s), 8.26(1H, s), 9.98(1H, s).
MS (ES-) : 309.20.

Example 22
5-[4-(2-Hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

The title compound (200mg, 58.8%) was prepared as

a powder from 5-(4-hydroxyphenyl)-4-(4-methoxypheny
l)-1,3-oxazole-2-carboxamide obtained by Example 21
(298mg, 0.96mmol) and chloroethanol (193mg, 2.4mmol)
in a similar manner to that of Example 87 described la
ter.

1H-NMR (300 MHz, $CDCl_3$) : δ 2.01(1H, t, J=7Hz), 3.85(3H,
s), 4.03(2H, dd, J=7,5Hz), 4.12(2H, t, J=5Hz), 5.14(1H,
br-s), 6.87-6.95(4H, m), 6.98(1H, br peak), 7.55(2H, d,
J=8Hz), 7.60(2H, d, J=8Hz).
MS (ES+) : 355.20.

Example 23

5-[4-(2-Hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3
-oxazole-2-carbonitrile

To a solution of 5-[4-(2-hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3
-oxazole-2-carboxamide obtained by Example 22 (55.4mg,
0.156mmol) and pyridine (61.8mg, 0.782mmol) in
dichloromethane (2mL) was added trifluoroacetic
anhydride (75.5mg, 0.36mmol) under nitrogen at room
temperature and the mixture was stirred at the same
temperature for 1hr.

The mixture was evaporated in vacuo and the residue
was partitioned between water and ethyl acetate. The
organic layer was separated, washed with 1mol/L
hydrochloric acid and water, dried over magnesium sulfate
and evaporated in vacuo.

The residue was dissolv d in methanol (5mL) and the

solution was allowed to stand at room temp rature for 18hrs.

After evaporation of solvent, the residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=1:1) and triturated with a mixture of petroleum ether and diethyl ether to give the title compound (26 mg, 49.4%) as a powder.

1H-NMR (300 MHz, $CDCl_3$) : δ 2.00(1H, t, J=7Hz), 3.85(3H, s), 4.00(2H, dd, J=7,5Hz), 4.14(2H, t, J=5Hz), 6.93(2H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.51-7.60(4H, m).
MS (ES+) : 337.15.

Example 24

2-{4-[2-(Aminocarbonyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl acetate

The title compound (102mg, 85.2%) was prepared as an oil from 5-[4-(2-hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 22 (107mg, 0.302mmol) in a similar manner to that of Example 39-1 described later.

1H-NMR (300 MHz, $CDCl_3$) : δ 2.11(3H, s), 3.85(3H, s), 4.20(2H, t, J=5Hz), 4.44(2H, t, J=5Hz), 5.66(1H, br s), 6.91(2H, d, J=8Hz), 6.93(2H, d, J=8Hz), 6.99(1H, br s), 7.55(2H, d, J=8Hz), 7.60(2H, d, J=8Hz).
MS (ES+) : 397.12.

Example 25

2-{4-[2-Cyano-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl acetate

The title compound (80mg, 83.8%) was prepared as an oil from 2-{4-[2-(aminocarbonyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl acetate obtained by Example 24 (100mg, 0.252mmol) in a similar manner to that of Example 3.

1H-NMR (300 MHz, $CDCl_3$) : δ 2.11(3H, s), 3.85(3H, s), 4.23(2H, t, J=5Hz), 4.45(2H, t, J=5Hz), 6.89-6.99(4H, m), 7.50-7.60(4H, m).

Example 26

5-[4-(Cyanomethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

The title compound (383mg, 86.6%) was prepared as an oil from 5-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 21 (393 mg, 1.27mmol) and iodoacetonitrile (423mg, 2.53mmol) in a similar manner to that of Example 13.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.86(3H, s), 4.81(2H, s), 5.65(1H, br-s), 6.91-7.04(5H, m), 7.55(2H, d, J=8Hz), 7.68(2H, d, J=8Hz).
MS (ES+) : 350.11.

Example 27

5-[4-(2-Aminoethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-o

xazole-2-carboxamide

To a mixture of 5-[4-(cyanomethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 26 (150mg, 0.429mmol) and cobalt(II) chloride hexahydrate (30.6mg, 0.129mmol) in methanol (3mL) was added sodium borohydride (162mg, 4.29mmol) portionwise in water bath under nitrogen and the mixture was stirred in water bath for 15min. 1N Sodium hydroxide solution (0.5mL) was added to the mixture and the reaction mixture was stirred for 30min.

The reaction mixture was filtered through Celite and evaporated in vacuo. The residue was partitioned between water and chloroform. The organic layer was separated, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (chloroform : methanol=10:1) to give the title compound (77mg, 50.7%) as a powder.

1H-NMR (300MHz, $CDCl_3$) : δ 3.11(2H, t, J=5Hz), 3.85(3H, s), 4.02(2H, t, J=5Hz), 5.61(1H, br-s), 6.90(2H, d, J=8Hz), 6.93(2H, d, J=8Hz), 6.99(1H, br-s), 7.56(2H, d, J=8Hz), 7.60(2H, d, J=8Hz).

Example 28

5-{4-[2-(Acetylamino)ethoxy]phenyl}-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

The title compound (47mg, 60%) was prepared as an oil from 5-[4-(2-aminoethoxy)phenyl]-4-(4-methoxyphen

yl)-1,3-oxazole-2-carboxamide obtained by Example 27 (70mg, 0.198mmol) in a similar manner to that of Example 39-1 described later.

1H-NMR (300MHz, $CDCl_3$) : δ 2.03(3H, s), 3.70(2H, q, J=5Hz), 3.85(3H, s), 4.07(2H, t, J=5Hz), 5.96(1H, br-s), 6.10(1H, br-s), 6.89(2H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.11(1H, br-s), 7.54(2H, d, J=8Hz), 7.60(2H, d, J=8Hz).
MS (ES+) : 396.13.

Example 29

N-(2-{4-[2-Cyano-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)acetamide

The title compound (26mg, 56.2%) was prepared as a powder from 5-{4-[2-(acetylamino)ethoxy]phenyl}-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 28 (48.5mg, 0.123mmol) in a similar manner to that of Example 23.

1H-NMR (300MHz, $CDCl_3$) : δ 2.05(3H, s), 3.69(2H, q, J=5Hz), 3.85(3H, s), 4.09(2H, t, J=5Hz), 5.91(1H, br peak), 6.88-6.96(4H, m), 7.50-7.60(4H, m).
MS (ES+) : 378.10.

Example 30-1

(2E)- and (2Z)-2-[4-(Benzyloxy)phenyl]-3-(6-methoxy-3-pyridinyl)-2-propenoic acid

The title compound was prepared in a similar manner

to that of Example 91-3 described later.

1H-NMR (300 MHz, DMSO-d6) : 3.81(15/8H, s), 3.87(9/8H, s), 5.13(10/8H, s), 5.15(6/8H, s), 6.64(5/8H, d, J=8Hz), 6.86(3/8H, d, J=8Hz), 6.93(3/8H, s), 7.03-7.12(2H, m), 7.18(5/8H, dd, J=8,2Hz), 7.32-7.50(7H, m), 7.70(5/8H, s), 7.80(3/8H, dd, J=8,2Hz), 8.04(5/8H, d, J=2Hz), 8.28(3/8H, d, J=2Hz).

Example 30-2
1-[4-(Benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)ethanone

The title compound was prepared from (2E)- and (2Z)-2-[4-(benzyloxy)phenyl]-3-(6-methoxy-3-pyridinyl)-2-propenoic acid obtained by Example 30-1 in a similar manner to that of Example 91-4 described later.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.92(3H, s), 4.16(2H, s), 5.14(2H, s), 6.72(1H, d, J=8Hz), 7.02(2H, d, J=8Hz), 7.30-7.45(5H, m), 7.49(1H, dd, J=8,2Hz), 7.99(2H, d, J=8Hz), 8.02(1H, d, J=2Hz).
MS (ES+) : 334.15.

Example 30-3
1-[4-(Benzyloxy)phenyl]-2-bromo-2-(6-methoxy-3-pyridinyl)ethanone

Th title compound (21.2g, 78.1%) was prepared as a powder from 1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3

-pyridinyl)ethanone (22g, 66mmol) and pyridinium tribromide (23.2g, 72.6mmol) in a similar manner to that of Example 68-1 described later.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.95(3H, s), 5.14(2H, s), 6.26(1H, s), 6.80(1H, d, J=8Hz), 7.02(2H, d, J=8Hz), 7.30-7.46(5H, m), 7.92(1H, dd, J=8,2Hz), 8.01(2H, d, J=8Hz), 8.21(1H, d, J=2Hz).
MS (ES+) : 411.98, 413.95.

Example 30-4
2-[2-[4-(Benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]-1H-isoindole-1,3(2H)-dione

The title compound (20.0g, 81.2%) was prepared as a powder from 1-[4-(benzyloxy)phenyl]-2-bromo-2-(6-methoxy-3-pyridinyl)ethanone obtained by Example 30-3 (21.2g, 51.5mmol) and potassium phthalimide (9.54g, 51.3mmol) in a similar manner to that of Example 9-2.

1H-NMR (300MHz, $CDCl_3$) : δ 3.91(3H, s), 5.07(2H, s), 6.65-6.72(2H, m), 6.93(2H, d, J=8Hz), 7.27-7.41(5H, m), 7.66-7.78(3H, m), 7.78-7.88(4H, m), 8.26(1H, d, J=2Hz).

Example 30-5
2-Amino-1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)ethanone hydrochloride

The title compound (2.67g, 110%) was prepared from 2-[2-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-

2-oxoethyl]-1H-isoindole-1,3(2H)-dione obtained by Example 30-4 (3.0g, 6.27mmol) in a similar manner to that of Example 9-3.

1H-NMR (300 MHz, DMSO-d6) : δ 3.82(3H, s), 5.18(2H, s), 6.32(1H, br peak), 6.85(1H, d, J=8Hz), 7.10(2H, d, J=8Hz), 7.26-7.50(5H, m), 7.71(1H, dd, J=8,2Hz), 8.02(2H, d, J=8Hz), 8.40(1H, d, J=2Hz), 8.91(2H, br peak).

Example 30-6

N-[2-[4-(Benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]-2,2-difluoroacetamide

To a solution of difluoroacetic acid (799mg, 8.33 mmol) in tetrahydrofuran (8mL) were added oxalyl chloride (1.06g, 8.33mmol) and N,N-dimethylformamide (1drop) at 0℃ under nitrogen and the mixture was stirred at room temperature for 1hr. The mixture was added to a mixture of 2-amino-1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)ethanone hydrochloride obtained by Example 30-5 (2.67g, 6.94mmol) and triethylamine (2.11g, 20.8mmol) in dichloromethane (25mL) at 0℃ and the reaction mixture was stirred at the same temperature for 2hrs.

The reaction mixture was evaporated in vacuo and partitioned between water and ethyl acetate. The organic layer was separated, washed with water, saturated sodium bicarbonate solution and brine, successively, dried over magnesium sulfate. After evaporation of solvent, the residue was purified by silica gel column chromatography

(n-hexane : ethyl acetate=3:1) to give the title compound (1.25g, 42.6%) as a powder.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.89(3H, s), 5.10(2H, s), 5.89(1H, t, J=53Hz), 6.40(1H, d, J=8Hz), 6.68(1H, d, J=8Hz), 6.96(2H, d, J=8Hz), 7.31-7.42(5H, m), 7.53(1H, dd, J=8,2Hz), 7.89-8.00(3H, m), 8.25(1H, d, J=2Hz).

Example 30-7

5-[5-[4-(Benzyloxy)phenyl]-2-(difluoromethyl)-1,3-oxazol-4-yl]-2-methoxypyridine

The title compound (840mg, 70.2%) was prepared as a powder from N-[2-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]-2,2-difluoroacetamide obtained by Example 30-6 (1.25g, 2.93mmol) in a similar manner to that of Example 9-5.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.97(3H, s), 5.10(2H, s), 6.70(1H, t, J=53Hz), 6.77(1H, d, J=8Hz), 7.00(2H, d, J=8Hz), 7.30-7.48(5H, m), 7.54(2H, d, J=8Hz), 7.82(1H, dd, J=8,2Hz), 8.44(1H, d, J=2Hz).

Example 31

4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenol

5-[5-[4-(Benzyloxy)phenyl]-2-(difluoromethyl)-1,3-oxazol-4-yl]-2-methoxypyridine obtained by Example 30-7 (830mg, 2.03mmol) and dry 20% palladium hydroxide

on carbon (240mg) in ethanol (8mL) and cyclohexene (4 mL) was stirred at reflux condition for 2hrs and cooled to room temperature.

After filtration, the reaction mixture was evaporated in vacuo to give the title compound (630mg, 97.8%) as a powder.

1H-NMR (300 MHz, DMSO-d6) : δ 3.89(3H, s), 6.86(2H, d, J=9Hz), 6.91(1H, d, J=9Hz), 7.30(1H, t, J=53Hz), 7.84(1H, dd, J=9,2Hz), 8.36(1H, d, J=2Hz).

Example 32

Ethyl {4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}acetate

The title compound (830mg, 105%) was prepared as a powder from 4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenol obtained by Example 31 (620mg, 1.95mmol) and ethyl bromoacetate (390mg, 2.34 mmol) in a similar manner to that of Example 11.

1H-NMR (300 MHz, $CDCl_3$) : δ 1.32(3H, t, J=7Hz), 3.97(3H, s), 4.28(2H, q, J=7Hz), 4.66(2H, s), 6.69(1H, t, J=53Hz), 6.78(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.80(1H, dd, J=8,2Hz), 8.42(1H, d, J=2Hz).
MS (ES+) : 405.11.

Example 33

2-{4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol

The title compound (630mg, 82.2%) was prepared as crystals from ethyl {4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}acetate (855 mg, 2.11mmol) obtained by Example 32 in a similar manner to that of Example 12.

MP : 126-128℃.

1H-NMR (300MHz, $CDCl_3$) : δ 2.01(1H, t, J=6Hz), 3.98(3H, s), 4.00(2H, dd, J=6,5Hz), 4.13(2H, t, J=5Hz), 6.70(1H, t, J=53Hz), 6.77(1H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.82(1H, dd, J=8,2Hz), 8.43(1H, d, J=2Hz).

MS (ES+) : 363.14.

Example 34

2-{4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate

To a solution of 2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 33 (203mg, 0.56mmol) and triethylamine (85mg, 0.84mmol) in dichloromethane (4mL) was added methanesulfonyl chloride (86.3mg, 0.84mmol) at 0℃ under nitrogen and the mixture was stirred at the same temperature for 2hrs.

The reaction mixture was evaporated in vacuo and the residue was partitioned between water and chloroform. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate

solution and brine, dried over magnesium sulfate, and evaporated in vacuo to give the title compound (247mg, 100.1%) as an oil.

1H-NMR (300MHz, $CDCl_3$) : δ 3.11(3H, s), 3.97(3H, s), 4.29(2H, t, J=5Hz), 4.60(2H, t, J=5Hz), 6.70(1H, t, J=53Hz), 6.78(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.82(1H, dd, J=8,2Hz), 8.41(1H, d, J=2Hz).

Example 35

2-(2-{4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

To a solution of 2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 34 (247mg, 0.561mmol) in N,N-dimethylformamide (5mL) was added potassium phthalimide (156mg, 0.841mmol) at room temperature and the mixture was stirred at 60℃ for 18hrs.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo to give the title compound (260mg, 94.3%) as an oil.

1H-NMR (300MHz, $CDCl_3$) : δ 3.96(3H, s), 4.13(1H, t, J=7Hz), 4.27(1H, t, J=7Hz), 6.69(1H, t, J=53Hz), 6.76(1H, d, J=8Hz), 6.91(2H, d, J=8Hz), 7.79(2H, d, J=8Hz),

7.70-7.81(3H, m), 7.84-7.91(2H, m), 8.39(1H, d, J=2Hz).

Example 36

2-{4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine

To a solution of 2-(2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 35 (260mg, 0.529mmol) in acetonitrile (5mL) was added hydrazine monohydrate (212mg, 4.23mmol) at room temperature and the mixture was stirred at 60℃ for 5hrs.

After cooling, the precipitate was filtered off. The filtrate was concentrated in vacuo to give the title compound (184mg, 96.2%) as an oil.

1H-NMR (300MHz, $CDCl_3$) : δ 3.11(2H, t, J=5Hz), 3.97(3H, s), 4.03(2H, t, J=5Hz), 6.70(1H, t, J=53Hz), 6.78(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.54(2H, d, J=8Hz), 7.82(1H, dd, J=8,2Hz), 8.43(1H, d, J=2Hz).
MS (ES+) : 362.13.

Example 37

N-(2-{4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound (46mg, 47.8%) was prepared as a powder from 2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 36 (86mg, 0.238mmol) in a similar manner

to that of Example 18.

1H-NMR (300MHz, DMSO-d6) : δ 3.28-3.40(2H, m), 3.89(3H, s), 4.00(2H, t, J=5Hz), 5.55(2H, s), 6.18(1H, t, J=5Hz), 6.92(1H, d, J=9Hz), 7.09(2H, d, J=9Hz), 7.33(1H, t, J=53Hz), 7.52(2H, d, J=9Hz), 7.83(1H, dd, J=9,2Hz), 8.37(1H, d, J=2Hz).
MS (ES+) : 405.13.

Example 38
N-(2-{4-[2-(Difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

To a solution of 2-{4-[2-(difluoromethyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 36 (80mg, 0.221mmol) and triethyl amine (27mg, 0.266mmol) in dichloromethane (2mL) was added methanesulfonyl chloride (30.4mg, 0.266mmol) at 0℃ under nitrogen and the mixture was stirred at the same temperature for 2hrs.

The reaction mixture was evaporated in vacuo and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=2:1) to give the title compound (52mg, 53.4%) as an oil.

H-NMR (300MHz, $CDCl_3$) : δ 3.04(3H, s), 3.58(2H, q, J=7Hz), 3.97(3H, s), 4.15(2H, t, J=7Hz), 4.76(1H, t, J=7Hz), 6.70(1H, t, J=53Hz), 6.78 (1H, d, J=8Hz), 6.92(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.81(1H, dd, J=8, 2Hz), 8.41(1H, d, J=2Hz).

MS (ES+) : 440.11.

Example 39-1

N-[2-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-2,2,2-trifluoroacetamide

To a suspension of 2-amino-1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)ethanone hydrochloride (1.56g, 4.14mmol) in dichloromethane (16mL) were added triethylamine (503mg, 4.97mmol) and trifluoroacetic anhydride (1.04g, 4.97mmol) at 0℃ under nitrogen and the mixture was stirred at room temperature for 2hrs.

The reaction mixture was evaporated in vacuo and partitioned between water and ethyl acetate. The organic layer was separated, washed with water, saturated sodium bicarbonate solution and brine, successively, dried over magnesium sulfate. After evaporation of solvent, the residue was triturated with hexane to give the title compound (1.20g, 65.3%) as a powder.

1H-NMR (300MHz, $CDCl_3$) : δ 3.76(3H, s), 5.09(2H, s), 6.35(1H, d, J=7Hz), 6.84(2H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.26-7.44(7H, m), 7.87-8.00(3H, m).

MS (ES-) : 442.26.

Example 39-2

5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazole

The title compound (860mg, 74.7%) was prepared as a powder from N-[2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-2,2,2-trifluoroacetamide obtained by Example 39-1 (1.2g, 2.71mmol) in a similar manner to that of Example 9-5.

1H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 5.11(2H, s), 6.80(2H, d, J=8Hz), 6.98(2H, d, J=8Hz), 7.26-7.46(5H, m), 7.51-7.60(4H, m).

Example 40

4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenol

The title compound (655mg, 96.6%) was prepared as a powder from 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazole obtained by Example 39-2 (60mg, 2.02 mmol) in a similar manner to that of Example 65.

1H-NMR (300MHz, DMSO-d6) : δ 3.79(3H, s), 6.85(2H, d, J=8Hz), 7.00(2H, d, J=8Hz), 7.42(2H, d, J=8Hz), 7.52(2H, d, J=8Hz).

MS (ES-) : 334.20.

Example 41

2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethanol

The title compound (742mg, 98.6%) was prepared as a powder from 4-[4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenol obtained by Example 40 (665mg, 1.95mmol) and 2-chloroethanol (958mg, 11.9mmol) in a similar manner to that of Example 87 described later.

MP : 98-100℃.

1H-NMR (300MHz, $CDCl_3$) : δ 2.00(1H, t, J=7Hz), 3.85(3H, s), 4.00(2H, dt, J=7,5Hz), 4.13(1H, t, J=5Hz), 6.91(2H, d, J=8Hz), 7.05(2H, d, J=8Hz), 7.51-7.61(4H, m).

Example 42

2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate

The title compound (895mg, 100%) was prepared as an oil from 2-{4-[4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 41 (742mg, 1.96mmol) in a similar manner to that of Example 34.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.12(3H, s), 3.87(3H, s), 4.30(2H, t, J=5Hz), 4.60(2H, t, J=5Hz), 6.87-6.99(4H, m), 7.53-7.63(4H, m).

Example 43

2-(2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

The title compound (1.03g, 103%) was prepared as a powder from 2-{4-[4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 42 (895mg, 1.96mmol) and potassium phthalimide (544mg, 2.93mmol) in a similar manner to that of Example 35.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.84(3H, s), 4.11(2H, t, J=5Hz), 4.26(2H, t, J=5Hz), 6.83-6.95(4H, m), 7.45-7.58(4H, m), 7.68-7.80(2H, m), 7.80-7.93(2H, m).

Example 44

2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethanamine

2-(2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 43 (1.03g, 2.03mmol) was dissolved in a solution of 40% methylamine in methanol (5 mL) at room temperature and the mixture was stirred at the same temperature for 1day.

The reaction mixture was evaporated in vacuo and the residue was partitioned between water and diethyl ether. The water layer was adjusted to pH10 with saturated sodium bicarbonate solution and extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residu was purified by silica

gel column chromatography (chloroform : methanol=40:1) to give the title compound (575mg, 75%) as an oil.

1H-NMR (300MHz, $CDCl_3$) : δ 3.09-3.20(2H, m), 3.85(3H, s), 4.05(2H, t, J=5Hz), 6.90(2H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.54(2H, d, J=8Hz), 7.56(2H, d, J=8Hz).
MS (ES+) : 379.12.

Example 45

N-(2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound (58mg, 52.1%) was prepared as a powder from 2-{4-[4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 44 (100mg, 0.264mmol) in a similar manner to that of Example 18.

1H-NMR (300 MHz, DMSO-d6) : δ 3.25-3.40(2H, m), 3.79(3H, s), 4.00(2H, t, J=5Hz), 5.55(2H, s), 6.19(1H, t, J=5Hz), 7.00(2H, d, J=8Hz), 7.06(2H, d, J=8Hz), 7.51(2H, d, J=8Hz), 7.55(2H, d, J=8Hz).

Example 46

N-(2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (64.9mg, 53.8%) was prepared a s a powder from 2-{4-[4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained

by Example 44 (100mg, 0.264mmol) in a similar manner to that of Example 38.

1H-NMR (300MHz, $CDCl_3$) : δ 3.03(3H, s), 3.53-3.61(2H, m), 3.84(3H, s), 4.15(2H, t, J=5Hz), 4.70-4.80(1H, m), 6.85-6.95(4H, m), 7.51-7.61(4H, m).
MS (ES-) : 455.18.

Example 47

2-{4-[4-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethylamine hydrochloride

To a solution of 2-{4-[4-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 46 (288mg, 0.761mmol) in methanol (5mL) was added 10% hydrogen chloride in methanol (1mL) at room temperature. The reaction mixture was stirred at the same temperature for 30min.

The solution was evaporated in vacuo and the residue was washed with diethyl ether to give the title compound (302mg, 95.6%) as a yellow amorphous powder.

1H-NMR (300MHz, DMSO-d6) : δ 3.18-3.30(2H, m), 3.80(3H, s), 4.24(2H, t, J=5Hz), 7.01(2H, d, J=8Hz), 7.11(2H, d, J=8Hz), 7.51(2H, d, J=8Hz), 7.58 (2H, d, J=8Hz), 8.14(3H, br peak).

Example 48-1

N-[2-[4-(Benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]-2,2,2-trifluoroacetamide

The title compound (824mg, 42%) was prepar d as a powder from 2-amino-1-[4-(benzyloxy)phenyl]-2-(6-meth oxy-3-pyridinyl)ethanone hydrochloride obtained by Ex ample 30-5 (1.7g, 4.42mmol) and trifluoroacetic anhyd ride (1.21g, 5.74mmol) in a similar manner to that of Example 39-1.

1H-NMR (300MHz, $CDCl_3$) : δ 3.89(3H, s), 5.10(2H, s), 6.31-6.48(1H, m), 6.68(1H, d, J=8Hz), 6.96(2H, d, J=8Hz), 7.26-7.45(5H, m), 7.53(1H, dd, J=8,2Hz), 7.91(2H, d, J=8Hz), 8.26(1H, d, J=2Hz).

Example 48-2

5-[5-[4-(Benzyloxy)phenyl]-2-(trifluoromethyl)-1,3-ox azol-4-yl]-2-methoxypyridine

The title compound (607mg, 79.1%) was prepared as a powder from 5-[5-[4-(benzyloxy)phenyl]-2-(trifluor omethyl)-1,3-oxazol-4-yl]-2-methoxypyridine obtained by Example 48-1 (800mg, 1.8mmol) in a similar manner t o that of Example 9-5.

1H-NMR (300MHz, $CDCl_3$) : δ 3.97(3H, s), 5.11(2H, s), 6.78(1H, d, J=8Hz), 7.00(2H, d, J=8Hz), 7.30-7.49(5H, m), 7.54(2H, d, J=8Hz), 7.84(1H, dd, J=8,2Hz), 8.44(1H, d, J=2Hz).
MS (ES+) : 427.12.

Example 49

4-[4-(6-M thoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenol

The title compound (423mg, 88.4%) was prepared as a powder from 5-[5-[4-(benzyloxy)phenyl]-2-(trifluoromethyl)-1,3-oxazol-4-yl]-2-methoxypyridine obtained by Example 48-2 (607mg, 1.42mmol) in a similar manner to that of Example 31.

1H-NMR (300MHz, $CDCl_3$) : δ 3.97(3H, s), 6.81(1H, d, J=8Hz), 6.88(2H, d, J=8Hz), 7.49(2H, d, J=8Hz), 7.89(1H, dd, J=8,2Hz), 8.43(1H, d, J=2Hz).
MS (ES-) : 335.12.

Example 50
2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethanol

The title compound (305mg, 65.8%) was prepared as a powder from 4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenol obtained by Example 49 (410mg, 1.22mmol) and 2-chloroethanol (584mg, 7.32 mmol) in a similar manner to that of Example 87 described later.

1H-NMR (300MHz, $CDCl_3$) : δ 1.99(1H, t, J=7Hz), 3.97(3H, s), 3.99(2H, dt, J=7,5Hz), 4.12(1H, t, J=5Hz), 6.79(1H, d, J=8Hz), 6.96(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.84(1H, dd, J=8,2Hz), 8.44(1H, d, J=2Hz).
MS (ES+) : 381.08.

Example 51

2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate

The title compound (355mg, 99.8%) was prepared as an oil from 2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 50 (295mg, 0.776mmol) in a similar manner to that of Example 34.

1H-NMR (300MHz, $CDCl_3$) : δ 3.11(3H, s), 3.97(3H, s), 4.29(2H, t, J=5Hz), 4.60(2H, t, J=5Hz), 6.80(1H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.84(1H, dd, J=8,2Hz), 8.41(1H, d, J=2 Hz).
MS (ES+) : 459.03.

Example 52

2-(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

The title compound (395mg, 100%) was prepared as a powder from 2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 51 (355mg, 0.774mmol) and potassium phthalimide (125mg, 1.16mmol) in a similar manner to that of Example 35.

1H-NMR (300MHz, $CDCl_3$) : δ 3.97(3H, s), 4.14(2H, t, J=5Hz),

4.28(2H, t, J=5Hz), 6.77(1H, d, J=9Hz), 6.92(2H, d, J=9Hz), 7.50(2H, d, J=9Hz), 7.69-7.91(5H, m), 8.39(1H, d, J=2Hz).

Example 53

2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethylamine

The title compound (153mg, 53.4%) was prepared as an oil from 2-(2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 52 (385mg, 0.756mmol) in a similar manner to that of Example 36.

1H-NMR (300MHz, $CDCl_3$) : δ 3.11(2H, t, J=5Hz), 3.97(3H, s), 4.03(2H, t, J=5Hz), 6.79(1H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.54(2H, d, J=8Hz), 7.84(1H, dd, J=8,2Hz), 8.44(1H, d, J=2Hz).

Example 54

N-(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (53mg, 61.3%) was prepared as an oil from 2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 53 (71.7mg, 0.189mmol) in a similar manner to that of Example 38.

1H-NMR (300MHz, $CDCl_3$) : δ 3.04(3H, s), 3.59(2H, dd, J=6,5Hz), 3.97(3H, s), 4.15(2H, t, J=5Hz), 4.75(1H, t,

J=6Hz), 6.80(1H, d, J=8Hz), 6.93(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.84(1H, dd, J=8,2Hz), 8.42(1H, d, J=2Hz).

Example 55

N-(2-{4-[4-(6-Methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound (52mg, 59.6%) was prepared as a powder from 2-{4-[4-(6-methoxy-3-pyridinyl)-2-(trifluoromethyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 53 (79.3mg, 0.201mmol) in a similar manner to that of Example 18.

1H-NMR (300MHz, $CDCl_3$: CD_3OD=10:1) : δ 3.58(2H, t, J=5Hz), 3.97(3H, s), 4.07(2H, t, J=5Hz), 6.81(2H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.53(2H, d, J=8Hz), 7.85(1H, dd, J=8,2Hz), 8.40(1H, d, J=2Hz).
MS (ES+) : 423.15.

Example 56-1

N-[2-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethyl]-2-methylpropanamide

The title compound (688mg, 63.3%) was prepared as a powder from 2-amino-1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)ethanone hydrochloride obtained by Example 9-3 (1.0g, 2.61mmol) and isobutyryl chloride (333mg, 3.13mmol) in a similar manner to that of Example 7-7.

1H-NMR (300MHz, $CDCl_3$) : δ 1.12(3H, d, J=7.5Hz), 1.16(3H,

d, J=7.5Hz), 2.34-2.51(1H, m), 3.75(3H, s), 5.08(2H, s), 6.44(1H, d, J=7Hz), 6.81(2H, d, J=8Hz), 6.93(2H, d, J=8Hz), 6.98(1H, d, J=7Hz), 7.26-7.41(7H, m), 7.94(2H, d, J=8Hz).
MS (ES+) : 418.16.

Example 56-2
5-[4-(Benzyloxy)phenyl]-2-isopropyl-4-(4-methoxypheny l)-1,3-oxazole

The title compound (422mg, 74.7%) was prepared as an oil from N-[2-[4-(benzyloxy)phenyl]-1-(4-methoxyp henyl)-2-oxoethyl]-2-methylpropanamide obtained by Ex ample 56-1 (590mg, 1.41mmol) in a similar manner to th at of Example 1-2.

1H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.06-3.24(1H, m), 3.83(3H, s), 5.09(2H, s), 6.89(2H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.29-7.45(5H, m), 7.45(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).
MS (ES+) : 400.25.

Example 57
4-[2-Isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]ph enol

The title compound (222mg, 67.9%) was prepared as a powder from 5-[4-(benzyloxy)phenyl]-2-isopropyl-4-(4-methoxyphenyl)-1,3-oxazole obtained by Example 56-2 (422mg, 1.06mmol) in a similar manner to that of Exa mple 31.

1H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.08-3.24(1H, m), 3.83(3H, s), 6.81(2H, d, J=9Hz), 6.88(2H, d, J=9Hz), 7.44(2H, d, J=9Hz), 7.54(2H, d, J=9Hz).

MS (ES+) : 310.24.

Example 58

2-{4-[2-Isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanol

The title compound (163mg, 66.4%) was prepared as a powder from 4-[2-isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol obtained by Example 57 (215mg, 0.695mmol) and 2-chloroethanol (336mg, 4.17mmol) in a similar manner to that of Example 87 described later.

1H-NMR (300MHz, $CDCl_3$) : δ 1.42(6H, d, J=7Hz), 2.05(1H, t, J=6Hz), 3.04-3.25(1H, m), 3.83(3H, s), 3.94-4.01(2H, m), 4.10(2H, t, J=5Hz), 6.85-6.94(4H, m), 7.50(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).

Example 59

2-{4-[2-Isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate

The title compound (132mg, 101%) was prepared as an oil from 2-{4-[2-isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 58 (107mg, 0.303mmol) in a similar manner to that of Example 34.

1H-NMR (300MHz, $CDCl_3$) : δ 1.42(6H, d, J=7Hz), 3.10(3H, s), 3.11-3.25(1H, m), 3.83(3H, s), 4.24-4.30(2H, m), 4.55-4.61(2H, m), 6.84-6.92(4H, m), 7.50(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).

MS (ES+) : 432.15.

Example 60

2-(2-{4-[2-Isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

The title compound (150mg, 103%) was prepared as an oil from 2-{4-[2-isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 59 (130mg, 0.301mmol) and potassium phthalimide (83.7mg, 0.452mmol) in a similar manner to that of Example 35.

1H-NMR (300MHz, $CDCl_3$) : δ 1.40(6H, d, J=7Hz), 3.06-3.18(1H, m), 3.81(3H, s), 4.11(2H, t, J=5Hz), 4.24(2H, t, J=5Hz), 6.80-6.91(4H, m), 7.45(2H, d, J=9Hz), 7.52(2H, d, J=9Hz), 7.70-7.79(2H, m), 7.83-7.90(2H, m).

Example 61

2-{4-[2-Isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylamine

The title compound (106mg, 96.8%) was prepared as an oil from 2-(2-{4-[2-isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-

dione obtained by Example 60 (150mg, 0.311mmol) in a similar manner to that of Example 36.

1H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.06-3.21(1H, m), 3.83(3H, s), 4.00(2H, t, J=5Hz), 6.81-6.93(4H, m), 7.47(2H, d, J=9Hz), 7.54(2H, d, J=9 Hz).

Example 62

N-(2-{4-[2-Isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (23mg, 43.8%) was prepared as a powder from 2-{4-[2-isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 61 (43mg, 0.122mmol) in a similar manner to that of Example 38.

1H-NMR (300MHz, $CDCl_3$) : δ 1.42(6H, d, J=7Hz), 3.04(3H, s), 3.08-3.22(1H, m), 3.56(2H, q, J=5Hz), 3.83(3H, s), 4.12(2H, t, J=5Hz), 4.75(1H, br peak), 6.85(2H, d, J=9Hz), 6.90(2H, d, J=9Hz), 7.50(2H, d, J=9Hz), 7.54(2H, d, J=9 Hz).
MS (ES+) : 431.13.

Example 63

N-(2-{4-[2-Isopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound (23mg, 32.5%) was prepared as an oil from 2-{4-[2-isopropyl-4-(4-m thoxyphenyl)-1,3

-oxazol-5-yl]phenoxy}ethylamine obtained by Example 62 (63mg, 0.179mmol) in a similar manner to that of Example 18.

1H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.08-3.21(1H, m), 3.61(2H, q, J=5Hz), 3.83(3H, s), 4.05(2H, t, J=5Hz), 4.40(2H, br-s), 4.95(1H, br peak), 6.85(2H, d, J=9Hz), 6.89(2H, d, J=9Hz), 7.49(2H, d, J=9Hz), 7.54(2H, d, J=9Hz).

MS (ES+) : 396.20.

Example 64-1

1,2-Bis(4-methoxyphenyl)-2-oxoethyl (benzyloxy)acetate

To a solution of anisoin (500mg, 1.84mmol) and pyridine (581mg, 7.34mmol) in dichloromethane (10mL) was added benzyloxyacetyl chloride (424mg, 2.30mmol) under nitrogen at room temperature and the mixture was stirred at the same temperature for 22hrs.

The mixture was pored into 1mol/L hydrochloric acid and extracted with chloroform. The organic layer was washed with 1mol/L hydrochloric acid and water, dried over magnesium sulfate and evaporated in vacuo to give the title compound (775 mg, 100.4%) as an oil.

1H-NMR (300MHz, $CDCl_3$) : δ 3.78(3H, s), 3.83(3H, s), 4.21(1H, d, J=17Hz), 4.32(1H, d, J=17Hz), 4.68(2H, s), 6.82-6.92(5H, m), 7.21-7.42(7H, m), 7.91(2H, d, J=8Hz).

Example 64-2

2-[(Benzyloxy)methyl]-4,5-bis(4-methoxyphenyl)-1,3-oxazole

To a solution of 1,2-bis(4-methoxyphenyl)-2-oxoethyl (benzyloxy)acetate obtained by Example 64-1 (775mg, 1.84mmol) in acetic acid (14mL) was added ammonium acetate (1.42g, 18.4mmol) at room temperature and the mixture was heated to reflux with stirring for 1hr.

After cooling, the reaction mixture was evaporated in vacuo and acetic acid was azeotropically removed with toluene. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water, saturated sodium bicarbonate solution and brine, successively, dried over magnesium sulfate. After evaporation of solvent, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=4:1) and triturated with ethanol to give the title compound (300mg, 40.5%) as a pale yellow powder.

1H-NMR (300MHz, $CDCl_3$) : δ 3.84(6H, s), 4.67(2H, s), 4.70(2H, s), 6.84-6.94(4H, m), 7.26-7.44(5H, m), 7.51(2H, d, J=8Hz), 7.56(2H, d, J=8Hz).

MS (ES+) : 402.12.

Example 65

[4,5-Bis(4-methoxyphenyl)-1,3-oxazol-2-yl]methanol

A mixture of 2-[(benzyloxy)methyl]-4,5-bis(4-methoxyphenyl)-1,3-oxazole obtained by Example 64-2 (88mg,

0.219mmol) and 10% palladium on carbon (20mg) in a mixture of methanol (2mL) and tetrahydrofuran (2mL) was stirred at room temperature under hydrogen for 6hrs.

The reaction mixture was filtered through Celite and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=1:1) and triturated with a mixture of hexane and diethyl ether to give the title compound (44mg, 65.4%) as a pale yellow powder.

1H-NMR (300MHz, $CDCl_3$) : δ 2.36(1H, t, J=7Hz), 3.84(6H, s), 4.79(2H, d, J=7Hz), 6.85-6.94(4H, m), 7.51(2H, d, J=8Hz), 7.56(2H, d, J=8Hz).
MS (ES+) : 312.13.

Example 66-1

1,2-Bis(4-methoxyphenyl)-2-oxoethyl ethyl malonate

The title compound (644mg, 90.8%) was prepared as an oil from anisoin (500mg, 1.84mmol) and ethyl 3-chloro-3-oxopropionate (346mg, 2.30mmol) in a similar manner to that of Example 64-1.

1H-NMR (300MHz, DMSO-d6) : δ 1.26(3H, t, J=7.5Hz), 3.53(2H, s), 3.79(3H, s), 3.83(3H, s), 4.20(2H, q, J=7.5Hz), 6.81-6.93(5H, m), 7.38(2H, d, J=8Hz), 7.91(2H, d, J=8Hz).

Example 66-2

Ethyl [4,5-bis(4-methoxyphenyl)-1,3-oxazol-2-yl]aceta

te

The title compound (186mg, 30.4%) was prepared an oil from 1,2-bis(4-methoxyphenyl)-2-oxoethyl ethyl malonate obtained by Example 66-1 (644mg, 1.67mmol) and ammonium acetate (1.28g, 16.7mmol) in a similar manner to that of Example 64-2.

1H-NMR (300 MHz, $CDCl_3$) : δ 1.31(3H, t, J=7.5Hz), 3.84(6H, s), 3.92(2H, s), 4.25(2H, q, J=7.5Hz), 6.90(4H, d, J=8Hz), 7.45-7.65(4H, m).
MS (ES+) : 368.14.

Example 67

[4,5-Bis(4-methoxyphenyl)-1,3-oxazol-2-yl]acetic acid

To a solution of ethyl [4,5-bis(4-methoxyphenyl)-1,3-oxazol-2-yl]acetate obtained by Example 66-2 (70mg, 0.191mmol) in ethanol (2mL) was added 1 mol/L sodium hydroxide solution (0.25mL) at room temperature and the mixture was stirred at the same temperature for 3hrs.

The reaction mixture was evaporated in vacuo and dissolved in water. The water solution was washed with ether, adjusted to pH1 with 6N hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with diethyl ether to give the title compound (31mg, 47.9%) as an amorphous powder.

1H-NMR (300MHz, DMSO-d6) : δ 3.63(2H, br-s), 3.77(3H, s), 3.79(3H, s), 6.95(2H, d, J=8Hz), 6.99(2H, d, J=8Hz), 7.43(2H, d, J=8Hz), 7.49(2H, d, J=8Hz).

MS (ES+) : 340.15.

Example 68-1

2-Bromo-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl) ethanone

To a solution of 2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone (1.0g, 3.89mmol) in dichloromethane (10mL) were added pyridinium tribromide (1.37g, 4.28mmol) and hydrogen bromide (33% solution in acetic acid, 1mL) at room temperature under nitrogen and the mixture was stirred at the same temperature for 40min.

The reaction mixture was evaporated in vacuo and acetic acid was azeotropically removed with toluene. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated in vacuo to give the title compound (1.32g, 101%) as an oil.

1H-NMR (300MHz, $CDCl_3$) : δ 3.80(3H, s), 3.99(3H, s), 6.29(1H, s), 6.77(1H, d, J=8Hz), 6.90(2H, d, J=8Hz), 7.45(2H, d, J=8Hz), 8.16(1H, dd, J=8,2Hz), 8.80(1H, d, J=2 Hz).

Example 68-2

2-Hydroxy-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridiny

1)ethanone

2-Bromo-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone obtained by Example 68-1 (1.30g, 3.87mmol) was dissolved in acetone (10mL) and water (5mL) and heated to reflux for 1hr.

The reaction mixture was evaporated in vacuo and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=2:1) to give the title compound (770mg, 72.9%) as an oil.

1H-NMR (300MHz, $CDCl_3$) : δ 3.77(3H, s), 3.96(3H, s), 4.46(1H, d, J=7Hz), 5.80(1H, d, J=7Hz), 6.74(1H, d, J=8Hz), 6.86(2H, d, J=8Hz), 7.25(2H, d, J=8Hz), 8.10(1H, dd, J=8,2Hz), 8.72(1H, d, J=2Hz).

Example 68-3

1-(4-Methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl methoxyacetate

The title compound (128mg, 101.3%) was prepared as an oil from 2-hydroxy-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone obtained by Example 68-2 (100mg, 0.366mmol) and methoxyacetyl chloride (47.7mg, 0.439mmol) in a similar manner to that of Example 64-1.

1H-NMR (300MHz, $CDCl_3$) : δ 3.48(3H, s), 3.88(3H, s),

3.96(3H, s), 4.16(1H, d, J=17Hz), 4.25(1H, d, J=17Hz), 6.74(1H, d, J=8Hz), 6.80(1H, s), 6.90(2H, d, J=8Hz), 7.36(2H, d, J=8Hz), 8.10(1H, dd, J=8,2Hz), 8.75(1H, d, J=2Hz).

Example 68-4

2-Methoxy-5-[2-(methoxymethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]pyridine

The title compound (80mg, 66.1%) was prepared as an oil from 1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl methoxyacetate obtained by Example 68-3 (128mg, 0.371mmol) and ammonium acetate (286mg, 3.71mmol) in a similar manner to that of Example 64-2.

1H-NMR (300MHz, $CDCl_3$) : δ 3.52(3H, s), 3.84(3H, s), 3.96(3H, s), 4.60(2H, s), 6.75(1H, d, J=8Hz), 6.90(2H, d, J=8Hz), 7.50(2H, d, J=8Hz), 7.83(1H, dd, J=8,2Hz), 8.42(1H, d, J=2Hz).

Example 69-1

1-(4-Methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl (acetyloxy)acetate

The title compound (990mg, 100.2%) was prepared as an oil from 2-hydroxy-2-(4-methoxyphenyl)-1-(6-methoxy-3-pyridinyl)ethanone obtained by Example 68-2 (725mg, 2.65mmol) and acetoxyacetyl chloride (542mg, 3.97mmol) in a similar manner to that of Example 64-1.

1H-NMR (300MHz, $CDCl_3$) : δ 2.15(3H, s), 3.79(3H, s), 3.96(3H, s), 4.74(1H, d, J=17Hz), 4.81(1H, d, J=17Hz), 6.74(1H, d, J=8Hz), 6.77(1H, s), 6.90(2H, d, J=8Hz), 7.37(2H, d, J=8Hz), 8.09(1H, dd, J=8,2Hz), 8.74(1H, d, J=2 Hz).

Example 69-2

[5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methyl acetate

The title compound (415mg, 48%) was prepared as an oil from 1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl (acetyloxy)acetate obtained by Example 69-1 (990mg, 2.65mmol) and ammonium acetate (2.04g, 26.5mmol) in a similar manner to that of Example 64-2.

1H-NMR (300MHz, $CDCl_3$) : δ 2.18(3H, s), 3.84(3H, s), 3.96(3H, s), 5.22(2H, s), 6.75(1H, d, J=8Hz), 6.91(2H, d, J=8Hz), 7.50(2H, d, J=8Hz), 7.83(1H, dd, J=8,2Hz), 8.42(1H, d, J=2Hz).

Example 70

[5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methanol

To a solution of [5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methyl acetate obtained by Example 69-2 (410mg, 1.26mmol) in methanol (8mL) was added potassium carbonate (208mg, 1.51mmol) at room temperature and the mixture was

stirr d at the same temperature for 1hr.

The reaction mixture was evaporated in vacuo and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=2:1) and triturated with isopropyl ether to give the title compound (247mg, 63.0%) as an amorphous powder.

1H-NMR (300MHz, $CDCl_3$) : δ 2.61(1H, t, J=7Hz), 3.84(3H, s), 3.97(3H, s), 4.80(2H, d, J=7Hz), 6.75(1H, d, J=8Hz), 6.90(2H, d, J=8Hz), 7.49(2H, d, J=8Hz), 7.81(1H, dd, J=8,2Hz), 8.42(1H, d, J=2Hz).
MS (ES+) : 313.06.

Example 71

5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carbaldehyde

A mixture of [5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]methanol obtained by Example 70 (192mg, 0.615mmol) and manganese(IV) oxide (187mg, 2.15mmol) in chloroform (5mL) was heated to reflux with stirring for 2hrs.

After cooling, the reaction mixture was filtered through Celite and evaporated in vacuo. The residue was triturated with petroleum ether to give the title compound (178mg, 93.3%) as an amorphous powder.

1H-NMR (300MHz, $CDCl_3$) : δ 3.86(3H, s), 3.99(3H, s), 6.81(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.62(2H, d, J=8Hz), 7.86(1H, dd, J=8,2Hz), 8.48(2H, d, J=8Hz), 9.78(1H, s).

Example 72

[5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl](phenyl)methanol

To a solution of 5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carbaldehyde obtained by Example 71 (70mg, 0.226mmol) in tetrahydrofuran (3mL) was added 3N solution of phenylmagunesium bromide in diethyl ether (0.1mL, 0.3mmol) dropwise at 0℃ under nitrogen and the mixture was stirred at the same temperature for 3hrs.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=2:1) to give the title compound (62.3mg, 71.1%) as an oil.

1H-NMR (300MHz, $CDCl_3$) : δ 3.30(1H, d, J=7Hz), 3.82(3H, s), 3.96(3H, s), 5.93(1H, d, J=7Hz), 6.75(1H, d, J=8Hz), 6.87(2H, d, J=8Hz), 7.32-7.46(5H, m), 7.55(2H, d, J=8Hz), 7.83(1H, dd, J=8,2Hz), 8.41(1H, d, J=2Hz).

MS (ES+) : 389.10.

Example 73

[5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl](phenyl)methanone

The title compound (42mg, 70.4%) was prepared as yellow crystals from [5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl](phenyl)methanol obtained by Example 72 (60mg, 0.154mmol) in a similar manner to that of Example 71.

MP : 156-158℃.

1H-NMR (300MHz, $CDCl_3$) : δ 3.87(3H, s), 3.99(3H, s), 6.82(1H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.50-7.58(2H, m), 7.62-7.70(3H, m), 7.90(1H, dd, J=8,2Hz), 8.53-8.59(3H, m).

MS (ES+) : 387.05.

Example 74

5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxylic acid

To a suspension of 5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carbaldehyde obtained by Example 71 (103mg, 0.332mmol) in a mixture of water (0.8mL) and tert-buthylalcohol (3mL) were added 2-methyl-2-butene (103mg, 1.47mmol) and sodium dihydrogenphosphate (43.8mg, 0.365mmol) in water bath. To the mixture was added sodium chlorite (133mg, 1.47mmol) portionwise and stirred in

water bath for 1.5hrs.

The reaction mixture was evaporated in vacuo, dissolved in water. The solution was adjusted to pH4 with 1mol/L hydrochloric acid and extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated in vacuo to give the title compound (110mg, 101.6%) as an amorphous powder.

1H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 3.97(3H, s), 6.80(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.58(2H, d, J=8Hz), 7.87(2H, d, J=8Hz), 8.44(1H, s).
MS (ES+) : 327.03.

Example 75

5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide

A mixture of 5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxylic acid obtained by Example 74 (110mg, 0.337mmol), 1-hydroxybenzotriazole (61.5mg, 0.455mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (84mg, 0.438mmol) in N,N-dimethylformamide (6mL) was added ammonia solution (28%, 27mg, 0.438mmol) at 0℃ and the mixture was stirred at the same temperature for 18hrs.

The mixture was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated in vacuo to give the title compound

Exampl 73

[5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl](phenyl)methanone

The title compound (42mg, 70.4%) was prepared as yellow crystals from [5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl](phenyl)methanol obtained by Example 72 (60mg, 0.154mmol) in a similar manner to that of Example 71.

MP : 156-158℃.

1H-NMR (300MHz, $CDCl_3$) : δ 3.87(3H, s), 3.99(3H, s), 6.82(1H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.50-7.58(2H, m), 7.62-7.70(3H, m), 7.90(1H, dd, J=8,2Hz), 8.53-8.59(3H, m).

MS (ES+) : 387.05.

Example 74

5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxylic acid

To a suspension of 5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carbaldehyde obtained by Example 71 (103mg, 0.332mmol) in a mixture of water (0.8mL) and tert-buthylalcohol (3mL) were added 2-methyl-2-butene (103mg, 1.47mmol) and sodium dihydrogenphosphate (43.8mg, 0.365mmol) in water bath. To the mixture was added sodium chlorite (133mg, 1.47mmol) portionwise and stirred in

water bath for 1.5hrs.

The reaction mixture was evaporated in vacuo, dissolved in water. The solution was adjusted to pH4 with 1mol/L hydrochloric acid and extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated in vacuo to give the title compound (110mg, 101.6%) as an amorphous powder.

1H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 3.97(3H, s), 6.80(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.58(2H, d, J=8Hz), 7.87(2H, d, J=8Hz), 8.44(1H, s).
MS (ES+) : 327.03.

Example 75

5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide

A mixture of 5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxylic acid obtained by Example 74 (110mg, 0.337mmol), 1-hydroxybenzotriazole (61.5mg, 0.455mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (84mg, 0.438mmol) in N,N-dimethylformamide (6mL) was added ammonia solution (28%, 27mg, 0.438mmol) at 0℃ and the mixture was stirred at the same temperature for 18hrs.

The mixture was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonat solution and brine, dried over magnesium sulfate and evaporated in vacuo to give the title compound

(110mg, 100.3%) as an amorphous powder.

1H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 3.98(3H, s), 5.69(1H, br s), 6.79(1H, d, J=8Hz), 6.89-7.02(3H, m), 7.59(2H, d, J=8Hz), 7.82(1H, dd, J=8,2Hz), 8.45(1H, d, J=2Hz).
MS (ES+) : 326.06.

Example 76

5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carbonitrile

The title compound (57mg, 54.9%) was prepared as an amorphous powder from 5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide obtained by Example 75 (110mg, 0.338mmol) in a similar manner to that of Example 3.

1H-NMR (300MHz, $CDCl_3$) : δ 3.86(3H, s), 3.98(3H, s), 6.80(1H, d, J=8Hz), 6.95(2H, d, J=8Hz), 7.54(2H, d, J=8Hz), 7.81(1H, dd, J=8,2Hz), 8.44(1H, d, J=2Hz).
MS (ES+) : 308.04.

Example 77

5-[2-(Difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]-2-methoxypyridine

To a solution of 5-(4-methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carbaldehyde obtained by Example 71 (100mg,

0.322mmol) in dichloromethane (2mL) was added diethylaminosulfur trifluoride (62.3mg, 0.51mmol) at 0℃ under nitrogen and the mixture was stirred at the same temperature for 3hrs.

The reaction mixture was partitioned between water and chloroform. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (toluene : ethyl acetate=9:1) and triturated with hexane to give the title compound (41mg, 38.3%) as an amorphous powder.

MP : 87-89℃.

1H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 3.97(3H, s), 6.71(1H, t, J=52Hz), 6.78(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.54(2H, d, J=8Hz), 7.82(1H, dd, J=8,2Hz), 8.44(1H, d, J=2Hz).

MS (ES+) : 333.08.

Example 78-1

Diphenyl anilino(4-cyanophenyl)methylphosphonate

To a solution of 4-formylbenzonitrile (175g) in isopropyl acetate (2.1L) was added potassium fluoride (77.5mg) followed by addition of aniline (124g), and the mixture was heated to 60℃ with stirring. To the mixture was added dropwise diphenyl phosphonate (469g) over 45min, and the mixture was heated at 60℃ for additional 30min.

To the mixture was added dropwise n-heptane (2.8L) over 2hrs, and the mixture was cooled to 15℃.

The resulting precipitate was collected by filtration, washed successively with water, 50% isopropyl acetate in n-heptane, and dried to give the title compound as crystals (494g, 84%).

1H-NMR (300MHz, DMSO-d6) : δ 5.70-6.00(1H, m), 6.61(1H, t, J=7Hz), 6.80-7.49(15H, m), 7.79-8.00(4H, m).

Example 78-2

4-[(4-Methoxyphenyl)acetyl]benzonitrile

To a mixture of diphenyl anilino(4-cyanophenyl)methylphosphonate obtained by Example 78-1 (493g) and 4-methoxybenzaldehyde (168g) in tetrahydrofuran (1.0L) and 2-propanol (2.8L) was added potassium tert-butoxide (138g) in tetrahydrofuran (1.8L) over 6hrs. The mixture was stirred for additional 30min. To the mixture was added dropwise 2N hydrochloric acid (2.0L), and the mixture was heated at 45℃ for 1hr.

The mixture was neutralized to pH 6 by adding 6N sodium hydroxide solution (700mL). The mixture was cooled to 5℃, and the resulting precipitate was collected by filtration, washed successively with 50% 2-propanol in cooled water, water, and dried to give the title compound as crystals (200g, 71%).

1H-NMR (300MHz, $CDCl_3$) : δ 3.78(3H, s), 4.23(2H, s), 6.87(2H, d, J=8.4Hz), 7.15(2H, d, J=8.4Hz), 7.74(2H, d,

J=8.2Hz), 8.07(2H, d, J=8.2Hz).

Example 78-3

4-[Bromo(4-methoxyphenyl)acetyl]benzonitrile

To a solution of 4-[(4-methoxyphenyl)acetyl]benzonitrile obtained by Example 78-2 (3.0g, 11.9mmol) in tetrahydrofuran (30mL) was added pyridinium tribromide (3.82g, 11.9mmol) portionwise at room temperature under nitrogen and the mixture was stirred at the same temperature for 1.5hrs.

The reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with hexane to give the title compound (3.77g, 95.6%) as a powder.

1H-NMR (300MHz, $CDCl_3$) : δ 3.81(3H, s), 6.24(1H, s), 6.91(2H, d, J=8Hz), 7.44(2H, d, J=8Hz), 7.75(2H, d, J=8Hz), 8.06(2H, d, J=8Hz).

Example 78-4

2-(4-Cyanophenyl)-1-(4-methoxyphenyl)-2-oxoethyl (acetyloxy)acetate

To a solution of 4-[bromo(4-methoxyphenyl)acetyl]benzonitrile obtained by Example 78-3 (500mg, 1.51mmol) in acetone were add d acetoxyacetic acid (179mg, 1.51mmol) and cesium carbonate

(493mg, 1.51mmol) at room temperature under nitrogen and the mixture was stirred at the same temperature for 18hrs.

The reaction mixture was evaporated in vacuo and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate=2:1) to give the title compound (337mg, 60.6%) as an oil.

1H-NMR (300MHz, $CDCl_3$) : δ 2.15(3H, s), 3.85(3H, s), 4.74(1H, d, J=16Hz), 4.82(1H, d, J=16Hz), 6.87-6.96(3H, m), 7.58(2H, d, J=9Hz), 7.68(2H, d, J=9Hz), 7.90(2H, d, J=9Hz).

MS (ES-) : 366.15.

Example 78-5

[4-(4-Cyanophenyl)-5-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl acetate

The title compound (250mg, 78.8%) was prepared as an oil from 2-(4-cyanophenyl)-1-(4-methoxyphenyl)-2-oxoethyl (acetyloxy)acetate obtained by Example 78-4 (335mg, 0.912mmol) and ammonium acetate (562mg, 7.3mmol) in a similar manner to that of Example 64-2.

1H-NMR (300MHz, $CDCl_3$) : δ 2.19(3H, s), 3.86(3H, s), 5.25(2H, s), 6.95(2H, d, J=8Hz), 7.53(2H, d, J=8Hz), 7.63(2H, d, J=8Hz), 7.71(2H, d, J=8Hz).

MS (ES+) : 349.03.

Example 79

4-[2-(Hydroxymethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]benzonitrile

The title compound (100mg, 45.5%) was prepared as a powder from 4-[2-(hydroxymethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]benzonitrile obtained by Example 78-5 (250mg, 0.718mmol) in a similar manner to that of Example 70.

MP : 151-153℃.

1H-NMR (300MHz, $CDCl_3$) : δ 2.50(1H, t, J=5Hz), 3.87(3H, s), 4.84(2H, d, J=5Hz), 6.95(2H, d, J=8Hz), 7.53(2H, d, J=8Hz), 7.62(2H, d, J=8Hz), 7.70(2H, d, J=8Hz).

MS (ES+) : 307.03.

Example 80-1

4-[1-Bromo-2-(4-methoxyphenyl)-2-oxoethyl]benzonitrile

The title compound (2.09g, 106%) was prepared as a powder from 4-[2-(4-methoxyphenyl)-2-oxoethyl]benzonitrile (1.5g, 5.97mmol) in a similar manner to that of Example 78-3.

1H-NMR (300MHz, $CDCl_3$) : δ 3.88(3H, s), 6.28(1H, s), 6.96(2H, d, J=8Hz), 7.67(4H, s), 7.98(2H, d, J=8Hz).

Example 80-2

1-(4-Cyanophenyl)-2-(4-methoxyphenyl)-2-oxoethyl methoxyacetate

The title compound (426mg, 82.9%) was prepared as an oil from 4-[1-bromo-2-(4-methoxyphenyl)-2-oxoethyl]benzonitrile obtained by Example 80-1 (500mg, 1.51mmol) and methoxyacetic acid (179mg, 1.51mmol) in a similar manner to that of Example 78-4.

1H-NMR (300MHz, $CDCl_3$) : δ 3.48(3H, s), 3.85(3H, s), 4.17(1H, d, J=15Hz), 4.25(1H, d, J=15Hz), 6.90(2H, d, J=8Hz), 6.95(1H, s), 7.59(2H, d, J=8Hz), 7.66(2H, d, J=8Hz), 7.91(2H, d, J=8Hz).

MS (ES-) : 338.18.

Example 80-3

4-[2-(Methoxymethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]benzonitrile

The title compound (188mg, 47.1%) was prepared as crystals from 1-(4-cyanophenyl)-2-(4-methoxyphenyl)-2-oxoethyl methoxyacetate obtained by Example 80-2 (423mg, 1.51mmol) in a similar manner to that of Example 64-2.

MP : 85-86℃.

1H-NMR (300MHz, $CDCl_3$) : δ 3.53(3H, s), 3.86(3H, s), 4.62(2H, s), 6.95(2H, d, J=8Hz), 7.54(2H, d, J=8Hz), 7.62(2H, d, J=8Hz), 7.73(2H, d, J=8Hz).

MS (ES+) : 321.08.

Example 81-1

2-(4-Cyanophenyl)-1-(4-methoxyphenyl)-2-oxoethyl methoxyacetate

The title compound (229mg, 89.1%) was prepared as an oil from 4-[bromo(4-methoxyphenyl)acetyl]benzonitrile obtained by Example 78-3 (250mg, 0.757mmol) and methoxyacetic acid (89.4mg, 0.757mmol) in a similar manner to that of Example 78-4.

1H-NMR (300MHz, $CDCl_3$) : δ 3.48(3H, s), 3.79(3H, s), 4.16(1H, d, J=15Hz), 4.25(1H, d, J=15Hz), 6.82(1H, s), 6.90(2H, d, J=8Hz), 7.34(2H, d, J=8Hz), 7.70(2H, d, J=8Hz), 7.96(2H, d, J=8Hz).

Example 81-2

4-[2-(Methoxymethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]benzonitrile

The title compound (47mg, 21.9%) was prepared as crystals from 2-(4-cyanophenyl)-1-(4-methoxyphenyl)-2-oxoethyl methoxyacetate obtained by Example 81-1 (227mg, 0.669mmol) in a similar manner to that of Example 64-2.

1H-NMR (300MHz, $CDCl_3$) : δ 3.52(3H, s), 3.86(3H, s), 4.60(2H, s), 6.94(2H, d, J=8Hz), 7.50(2H, d, J=8Hz), 7.62(2H, d, J=8Hz), 7.80(2H, d, J=8Hz).

MS (ES+) : 321.10.

Example 82-1

2-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-2-oxoethy
l (acetyloxy)acetate

The title compound (1.26g, 100%) was prepared as an oil from 1-[4-(benzyloxy)phenyl]-2-bromo-2-(4-meth oxyphenyl)ethanone obtained by Example 9-1 (1.24g, 2. 81mmol) and acetoxyacetic acid (332mg, 2.81mmol) in a similar manner to that of Example 78-4.

1H-NMR (300MHz, $CDCl_3$) : δ 2.14(3H, s), 3.78(3H, s), 4.72(1H, d, J=15Hz), 4.80(1H, d, J=15Hz), 5.08(2H, s), 6.85(1H, s), 6.87(2H, d, J=8Hz), 6.93(2H, d, J=8Hz), 7.30-7.43(7H, m), 7.89(2H, d, J=8Hz).

Example 82-2

[4-[4-(Benzyloxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxaz
ol-2-yl]methyl acetate

The title compound (1.2g, 99.5%) was prepared as an oil from 2-[4-(benzyloxy)phenyl]-1-(4-methoxypheny l)-2-oxoethyl (acetyloxy)acetate obtained by Example 82-1 (1.26g, 2.81mmol) and ammonium acetate (1.73g, 22. 5mmol) in a similar manner to that of Example 64-2.

1H-NMR (300MHz, $CDCl_3$) : δ 2.17(3H, s), 3.84(3H, s), 5.09(2H, s), 5.21(2H, s), 6.90(2H, d, J=8Hz), 6.93(2H, d, J=8Hz), 7.28-7.47(5H, m), 7.52(2H, d, J=8Hz), 7.56(2H,

d, J=8Hz).

Example 83

[4-[4-(Benzyloxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazol-2-yl]methanol

The title compound (570mg, 52.7%) was prepared as an oil from [4-[4-(benzyloxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazol-2-yl]methyl acetate obtained by Example 82-2 (1.2g, 2.79mmol) in a similar manner to that of Example 70.

1H-NMR (300MHz, $CDCl_3$) : δ 2.70(1H, br peak), 3.84(3H, s), 4.80(2H, s), 5.09(2H, s), 6.90(2H, d, J=8Hz), 6.98(2H, d, J=8Hz), 7.30-7.47(5H, m), 7.51(2H, d, J=8Hz), 7.56(2H, d, J=8Hz).

MS (ES+) : 388.06.

Example 84

4-[4-(Benzyloxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazole-2-carbaldehyde

The title compound (438mg, 77.2%) was prepared as a powder from [4-[4-(benzyloxy)phenyl]-5-(4-methoxyphenyl)-1,3-oxazol-2-yl]methanol obtained by Example 83 (570mg, 1.47mmol) in a similar manner to that of Example 71.

1H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 5.12(2H, s), 6.91(2H, d, J=8Hz), 7.02(2H, d, J=8Hz), 7.30-7.50(5H, m),

7.60(2H, d, J=8Hz), 7.65(2H, d, J=8Hz), 9.76(1H, s).

Example 85

4-[4-(Benzyloxy)phenyl]-2-(difluoromethyl)-5-(4-metho xyphenyl)-1,3-oxazole

The title compound (392mg, 76.5%) was prepared as a powder from 4-[4-(benzyloxy)phenyl]-5-(4-methoxyph enyl)-1,3-oxazole-2-carbaldehyde obtained by Example 84 (485mg, 1.26mmol) in a similar manner to that of Ex ample 77.

1H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 5.10(2H, s), 6.70(1H, t, J=53Hz), 6.92(2H, d, J=8Hz), 6.99(2H, d, J=8Hz), 7.29-7.49(5H, m), 7.53-7.61(4H, m).
MS (ES+) : 408.03.

Example 86

4-[2-(Difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenol

The title compound (279mg, 92.3%) was prepared as a powder from 4-[4-(benzyloxy)phenyl]-2-(difluoromet hyl)-5-(4-methoxyphenyl)-1,3-oxazole obtained by Exam ple 85 (388mg, 0.952mmol) in a similar manner to that of Example 65.

1H-NMR (300MHz, $CDCl_3$) : δ 3.85(3H, s), 5.10(1H, br-s), 6.70(1H, t, J=53Hz), 6.85(2H, d, J=8Hz), 6.92(2H, d, J=8Hz), 7.51(2H, d, J=8Hz), 7.56(2H, d, J=8Hz).

MS (ES-) : 316.25.

Example 87

2-{4-[2-(Difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenoxy}ethanol

To a solution of 4-[2-(difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenol obtained by Example 86 (120mg, 0.378mmol) in N,N-dimethylformamide (2mL) were added 2-chloroethanol (76.1mg, 0.946mmol), potassium iodide (157mg, 0.946mmol) and potassium carbonate (209mg, 1.51mmol) at room temperature and the mixture was stirred at 75℃ for 18hrs.

The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=2:3) to give the title compound (52.6mg, 38.5%) as an amorphous powder.

1H-NMR (300MHz, $CDCl_3$) : δ 2.03(1H, t, J=7Hz), 3.85(3H, s), 3.94-4.03(2H, m), 4.13(2H, t, J=5Hz), 6.70(1H, t, J=53Hz), 6.92(2H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.51-7.60(4H, m).

Example 88

tert-Butyl 2-{4-[2-(difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenoxy}ethylcarbamate

To a solution of 4-[2-(difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenol obtained by Example 86 (208mg, 0.656mmol), N-(tert-butoxycarbonyl)-2-aminoethanol (127mg, 0.787mmol) and diethyl azodicarboxylate (171mg, 0.983mmol) in anhydrous tetrahydrofuran (2mL) was added dropwise a solution of triphenylphosphine (258mg, 0.983mmol) in anhydrous tetrahydrofuran (4mL) at room temperature and the mixture was stirred at the same temperature for 18hrs.

The mixture was evaporated in vacuo and the residue was purified by preparative thin layer chromatography (n-hexane : ethyl acetate=3:1) to give the title compound (138mg, 45.7%) as an oil.

1H-NMR (300MHz, $CDCl_3$) : δ 1.46(9H, s), 3.55(2H, q, J=5Hz), 3.85(3H, s), 4.05(2H, t, J=5Hz), 5.00(1H, br peak), 6.70(1H, t, J=52Hz), 6.86-6.95(4H, m), 7.51-7.60(4H, m).

Example 89

2-{4-[2-(Difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenoxy}ethanamine hydrochloride

The title compound (96mg, 81.9%) was prepared as an amorphous powder from tert-butyl 2-{4-[2-(difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenoxy}ethylcarbamate obtained by Example 88 (136mg, 0.295mmol) in a similar manner to that of Example 17.

1H-NMR (300MHz, DMSO-d6) : δ 3.24(2H, t, J=5Hz), 3.81(3H, s), 4.20(2H, t, J=5Hz), 7.01-7.10(4H, m), 7.30(1H, t, J=53Hz), 7.50(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 8.06(3H, br peak).

MS (ES+) : 361.09.

Example 90

N-(2-{4-[2-(Difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenoxy}ethyl)urea

The title compound (70mg, 87.2%) was prepared as an amorphous powder from 2-{4-[2-(difluoromethyl)-5-(4-methoxyphenyl)-1,3-oxazol-4-yl]phenoxy}ethanamine hydrochloride obtained by Example 89 (79mg, 0.199mmol) in a similar manner to that of Example 18.

1H-NMR (300MHz, DMSO-d6) : δ 3.26-3.40(2H, m), 3.81(3H, s), 3.98(2H, t, J=5Hz), 5.54(2H, s), 6.18(1H, t, J=5Hz), 7.00(2H, d, J=8Hz), 7.06(2H, d, J=8Hz), 7.30 (1H, t, J=52Hz), 7.46-7.55(4H, m).

MS (ES+) : 404.07.

Example 91-1

Benzyl 2-(4-bromophenyl)ethyl ether

To a slurry of sodium hydride (abt. 60% oil suspension, 4.58g) in N,N-dimethylformamide (150mL) was added dropwise 2-(4-bromophenyl)ethanol (20g) in N,N-dimethylformamide (50mL) at 0℃, and the mixture was

stirred for 1hr at room temperature. To the mixture was added dropwise benzyl bromide (19.6g) at 0℃, and the mixture was stirred at room temperature for 6hrs.

The resulting mixture was partitioned between saturated aqueous ammonium chloride and ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give the title compound as a colorless oil (29.0g, 100%).

1H-NMR (300MHz, $CDCl_3$) : δ 2.88(2H, t, J=7Hz), 3.67(2H, t, J=7Hz), 4.52(2H, s), 7.11(2H, d, J=8Hz), 7.27-7.37(5H, m), 7.41(2H, d, J=8Hz).

Example 91-2

4-[2-(Benzyloxy)ethyl]benzaldehyde

To a solution of benzyl 2-(4-bromophenyl)ethyl ether obtained by Example 91-1 (29.0g) in dry tetrahydrofuran (300mL) was added dropwise n-butyllithium (1.57mol/L solution in hexanes, 66.5mL) at -78℃ under nitrogen, and the mixture was stirred at -78℃ for 1hr. To the mixture was added dropwise N,N-dimethylformamide (15.4mL).

After being stirred for 1.5hrs at -78℃, the mixture was warmed to room temperature and then poured into saturated aqueous ammonium chloride and three times extracted with ether. The combined organic extracts were washed with water, brine, dried over anhydrous magnesium sulfate and concentrated to give the title compound as a yellow oil (23.9g, 100%).

1H-NMR (300MHz, $CDCl_3$) : δ 3.02(2H, t, J=7Hz), 3.74(2H, t, J=7Hz), 4.53(2H, s), 7.37-7.27(5H, m), 7.41(2H, d, J=8Hz), 7.82(2H, d, J=8H), 10.00(1H, s).

Example 91-3

(2E)- and (2Z)-3-{4-[2-(Benzyloxy)ethyl]phenyl}-2-(4-methoxyphenyl)-2-propenoic acid

A mixture of 4-[2-(benzyloxy)ethyl]benzaldehyde obtained by Example 91-2 (23.9g) and 4-methoxyphenylacetic acid (16.5g) in acetic anhydride (30mL) and triethylamine (17mL) was heated under reflux with stirring for 8hrs.

After cooling, the mixture was concentrated and partitioned between 1N sodium hydroxide solution (500mL) and ether. The ether layer was discarded. The aqueous layer was acidified with 1mol/L hydrochloric acid. The resulting precipitate was collected by filtration, washed with water, and dried to give the title compound as crystals (19.8g, 51.2%).

1H-NMR (300MHz, DMSO-d6, a mixture of E- and Z-isomers) : δ 2.78(2H×0.76, t, J=7Hz), 2.86(2H×0.24, t, J=7Hz), 3.59(2H×0.76, t, J=7Hz), 3.66(2H×0.24, t, J=7Hz), 3.78(3H×0.76, s), 3.78(3H×0.24, s), 4.44(2H×0.76, s), 4.49(2H×0.24, s), 6.91-7.69(14H, m).
MS(ESI) : 389.09(M+H), 387.22(M-H).

Example 91-4

2-{4-[2-(Benzyloxy)ethyl]phenyl}-1-(4-methoxyphenyl)e

thanone

To a solution of (2E)- and (2Z)-3-{4-[2-(benzyloxy)ethyl]phenyl}-2-(4-methoxyphenyl)-2-propenoic acid obtained by Example 91-3 (19.4g) in 1,4-dioxane (200mL) was added triethylamine (7.66mL) followed by addition of diphenylphosphoryl azide (15.1g). The mixture was heated at 100℃ with stirring for 30min. To the mixture was added dropwise 50% acetic acid in water (200mL), and the mixture was heated at 100℃ for 1.5hrs.

After cooling, the mixture was concentrated, and the residue was neutralized with sodium hydrogencarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residual oil was dissolved in ethanol with stirring to give the title compound as crystals (12.3g, 68.3%).

1H-NMR (300MHz, $CDCl_3$) : δ 2.90(2H, t, J=7Hz), 3.67(2H, t, J=7Hz), 3.86(3H, s), 4.20(2H, s), 4.51(2H, s), 6.92(2H, d, J=9Hz), 7.18(4H , s), 7.24-7.34(5H , m), 7.99(2H, d, J=9Hz).
MS(ESI) : 361.13.

Example 91-5
2-{4-[2-(Benzyloxy)ethyl]phenyl}-2-bromo-1-(4-methoxyphenyl)ethanone

The title compound (4.3g, 100%) was prepared as an oil from 2-{4-[2-(benzyloxy)ethyl]phenyl}-1-(4-meth

oxyphenyl)ethanone obtained by Example 91-4 (3.5g, 9.71mmol) and pyridinium tribromide (3.42g, 10.7mmol) in a similar manner to that of Example 78-3.

1H-NMR (300MHz, $CDCl_3$) : δ 2.90(2H, t, J=7Hz), 3.66(2H, t, J=7Hz), 3.85(3H, s), 4.50(2H, s), 6.35(1H, s), 6.90(2H, d, J=8Hz), 7.15-7.35(7H, m), 7.44(2H, d, J=8Hz), 7.96(2H, d, J=8Hz).

Example 91-6

1-{4-[2-(Benzyloxy)ethyl]phenyl}-2-(4-methoxyphenyl)-2-oxoethyl (acetyloxy)acetate

The title compound (4.2g, 90.2%) was prepared as an oil from 2-{4-[2-(benzyloxy)ethyl]phenyl}-2-bromo-1-(4-methoxyphenyl)ethanone obtained by Example 91-5 (4.3g, 9.79mmol) and acetoxyacetic acid (1.16g, 9.79mmol) in a similar manner to that of Example 78-4.

1H-NMR (300MHz, $CDCl_3$) : δ 2.14(3H, s), 2.89(2H, t, J=7Hz), 3.64(2H, t, J=7Hz), 3.82(3H, s), 4.49(2H, s), 4.73(1H, d, J=15Hz), 4.80(1H, d, J=15Hz), 6.81-6.90(3H, m), 7.18-7.32(7H, m), 7.36(2H, d, J=8Hz), 7.90(2H, d, J=8Hz).

Example 91-7

[5-{4-[2-(Benzyloxy)ethyl]phenyl}-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methanol

To a solution of 1-{4-[2-(benzyloxy)ethyl]phenyl}-2-(4-methoxyphenyl)-

2-oxoethyl (acetyloxy)acetate obtained by Example 91-6 (4.2g, 8.83mmol) in acetic acid (40mL) was added ammonium acetate (5.44g, 70.6mmol) at room temperature and the mixture was heated to reflux with stirring for 4hrs.

After cooling, the reaction mixture was evaporated in vacuo and acetic acid was azeotropically removed with toluene. The residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with water, saturated sodium bicarbonate solution and brine, successively, dried over magnesium sulfate.

After evaporation of solvent, the residue was dissolved in methanol (20mL). To a solution was added potassium carbonate (610mg) at room temperature and the mixture was stirred at the same temperature for 1hr.

The reaction mixture was evaporated in vacuo and the residue was partitioned between water and ethyl acetate. The organic layer was separated, washed with 1mol/L hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (chloroform) to give the title compound (2.67g, 72.8%) as an oil.

1H-NMR (300MHz, $CDCl_3$) : δ 2.94(2H, t, J=7Hz), 3.70(2H, t, J=7Hz), 3.84(3H, s), 4.53(2H, s), 4.80(2H, s), 6.90(2H, d, J=8Hz), 7.15-7.39(7H, m), 7.50(2H, d, J=8Hz), 7.56(2H, d, J=8Hz).

Example 92

5-{4-[2-(Benzyloxy)ethyl]phenyl}-4-(4-methoxyphenyl)-

1,3-oxazole-2-carbaldehyde

The title compound (605mg, 22.8%) was prepared as an oil from [5-{4-[2-(benzyloxy)ethyl]phenyl}-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methanol obtained by Example 91-7 (2.37g, 6.43mmol) in a similar manner to that of Example 71.

1H-NMR (300MHz, $CDCl_3$) : δ 2.96(2H, t, J=7Hz), 3.73(2H, t, J=7Hz), 3.87(3H, s), 4.53(2H, s), 6.95(2H, d, J=8Hz), 7.20-7.40(7H, m), 7.55-7.67(4H, m), 9.79(1H, s).

Example 93

5-{4-[2-(Benzyloxy)ethyl]phenyl}-2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazole

The title compound (483mg, 75.8%) was prepared as an oil from 5-{4-[2-(benzyloxy)ethyl]phenyl}-4-(4-methoxyphenyl)-1,3-oxazole-2-carbaldehyde obtained by Example 92 (605mg, 1.46mmol) in a similar manner to that of Example 77.

1H-NMR (300MHz, $CDCl_3$) : δ 2.99(2H, t, J=7Hz), 3.71(2H, t, J=7Hz), 3.85(3H, s), 4.54(2H, s), 6.70(1H, t, J=53Hz), 6.91(2H, d, J=8Hz), 7.19-7.37(7H, m), 7.50-7.63(4H, m).

Example 94

2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethanol

The title compound (305mg, 80%) was prepared as a powder from 5-{4-[2-(benzyloxy)ethyl]phenyl}-2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazole obtained by Example 93 (481mg, 1.1mmol) in a similar manner to that of Example 31.

1H-NMR (300MHz, $CDCl_3$) : δ 1.41(1H, t, J=7Hz), 2.91(2H, t, J=7Hz), 3.85(3H, s), 3.90(2H, q, J=7Hz), 6.70(1H, t, J=53Hz), 6.92(2H, d, J=8Hz), 7.26(2H, d, J=8Hz), 7.54-7.62(4H, m).
MS (ES+) : 346.14.

Example 95
2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethyl methanesulfonate

The title compound (308mg, 100%) was prepared as an oil from 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethanol obtained by Example 94 (250mg, 0.724mmol) in a similar manner to that of Example 34.

1H-NMR (300MHz, $CDCl_3$) : δ 2.92(3H, s), 3.09(2H, t, J=7Hz), 3.85(3H, s), 4.45(2H, t, J=7Hz), 6.70(1H, t, J=53Hz), 6.93(2H, d, J=8Hz), 7.26(2H, d, J=8Hz), 7.55(2H, d, J=8Hz), 7.60(2H, d, J=8 Hz).

Example 96
2-(2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethyl)-1H-isoindole-1,3(2H)-dione

The title compound (365mg, 107%) was prepared as a powder from 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethyl methanesulfonate obtained by Example 95 (305mg, 0.72mmol) and potassium phthalimide (200mg, 1.08mmol) in a similar manner to that of Example 35.

1H-NMR (300MHz, $CDCl_3$) : δ 3.03(2H, t, J=7Hz), 3.85(3H, s), 3.95(2H, t, J=7Hz), 6.69(1H, t, J=53Hz), 6.90(2H, d, J=8Hz), 7.26(2H, d, J=8Hz), 7.49-7.58(4H, m), 7.68-7.74(2H, m), 7.80-7.86(2H, m).

Example 97

2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethylamine

The title compound (300mg, 115%) was prepared as an oil from 2-(2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 96 (360mg, 0.759mmol) in a similar manner to that of Example 44.

1H-NMR (300MHz, $CDCl_3$) : δ 2.68-2.90(4H, m), 3.85(3H, s), 6.70(1H, t, J=53Hz), 6.92(2H, d, J=9Hz), 7.15-7.30(2H, m), 7.44-7.64(4H, m).

Example 98

N-(2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethyl)methanesulfonamide

The title compound (78mg, 42.4%) was prepared as an oil from 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethylamine obtained by Example 97 (150mg, 0.434mmol) in a similar manner to that of Example 38.

1H-NMR (300MHz, $CDCl_3$) : δ 2.90(3H, s), 2.92(2H, t, J=7Hz), 3.44(2H, t, J=7Hz), 3.86(3H, s), 4.22(1H, t, J=6Hz), 6.71(1H, t, J=53Hz), 6.94(2H, d, J=8Hz), 7.25(2H, d, J=8Hz), 7.56(2H, d, J=8Hz), 7.60(2H, d, J=8Hz).
MS (ES-) : 421.19.

Example 99

N-(2-{4-[2-(Difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethyl)urea

The title compound (32mg, 19%) was prepared as a powder from 2-{4-[2-(difluoromethyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenyl}ethylamine obtained by Example 97 (150mg, 0.436mmol) in a similar manner to that of Example 18.

1H-NMR (300MHz, DMSO-d6) : δ 2.73(2H, t, J=7Hz), 3.22(2H, q, J=7Hz), 3.80(3H, s), 5.44(2H, s), 5.95(1H, t, J=6Hz), 7.00(2H, d, J=8Hz), 7.31(1H, t, J=53Hz), 7.33(2H, d, J=8Hz), 7.46-7.56(4H, m).
MS (ES+) : 388.15.

Example 100-1

2-[4-(Benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl) tha
none

1.56M n-Butyllithium in hexane (134mL, 209mmol) was added dropwise to a solution of 5-bromo-2-methoxypyridine (36.3g, 193mmol) in tetrahydrofuran (340mL) at -78℃ and the suspension stirred at the same temperature for 1hr. 2-[4-(Benzyloxy)phenyl]-N-methoxy-N-methylacetamide (55.1g, 193mmol) in tetrahydrofuran (340mL) was then added and stirring continued for a further 2.5hrs.

The mixture was allowed to 3℃ and then it was poured into NH_4Cl solution. The mixture was extracted with ethyl acetate (1000mL) and washed with brine. The organic extract was dried ($MgSO_4$) and the solvent was removed to give the title compound as solid. The solid was washed with isopropyl alcohol - isopropyl ether to give the title compound as white crystals.

1H-NMR (300 MHz, $CDCl_3$) : δ 3.99(3H, s), 4.16(2H, s), 5.04(2H, s), 6.78(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.18(2H, d, J=8Hz), 7.30-7.43(5H, m), 8.16(1H, dd, J=8,2Hz), 8.85(1H, d, J=2Hz).
MS (ES+) : 334.10.

Example 100-2
2-[4-(Benzyloxy)phenyl]-2-bromo-1-(6-methoxy-3-pyridi
nyl)ethanone

The title compound as an oil (1.87g, 100%) was pr
epared from 2-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-py

ridinyl)ethanone obtained by Exampl 100-1 (1.5g, 4.5 mmol) in a similar manner to that of Example 78-3.

1H-NMR (300MHz, $CDCl_3$) : δ 4.00(3H, s), 5.06(2H, s), 6.28(1H, s), 6.78(1H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.29-7.50(7H, m), 8.16(1H, dd, J=9,2Hz), 8.81(1H, d, J=2 Hz).

Example 100-3

1-[4-(Benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)-2-oxoethyl 2-methylpropanoate

The title compound (819mg, 43%) was prepared as an oil from 2-[4-(benzyloxy)phenyl]-2-bromo-1-(6-methoxy-3-pyridinyl)ethanone obtained by Example 100-2 (1.87g, 4.54mmol) and isobutyric acid (400mg, 4.54mmol) in a similar manner to that of Example 78-4.

1H-NMR (300MHz, $CDCl_3$) : δ 1.19(3H, d, J=7Hz), 1.26(3H, d, J=7Hz), 2.63-2.78(1H, m), 3.96(3H, s), 5.03(2H, s), 6.66(1H, s), 6.72(1H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.26-7.43(7H, m), 8.10(1H, dd, J=8,2Hz), 8.78(1H, d, J=2Hz).

Example 100-4

5-{5-[4-(Benzyloxy)phenyl]-2-isopropyl-1,3-oxazol-4-yl}-2-methoxypyridine

The title compound (562mg, 71.9%) was prepared as a powder from 1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3

-pyridinyl)-2-oxoethyl 2-methylpropanoate obtained by Example 100-3 (819mg, 1.95mmol) and ammonium acetate (1.2g, 15.6mmol) in a similar mann r to that of Exampl e 64-2.

1H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.09-3.21(1H, m), 3.96(3H, s), 5.09(2H, s), 6.75(1H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.29-7.51(7H, m), 7.81(1H, dd, J=9,2Hz), 8.40(1H, d, J=2Hz).

Example 101

4-[2-Isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenol

The title compound (410mg, 97.6%) was prepared as a powder from 5-{5-[4-(benzyloxy)phenyl]-2-isopropyl-1,3-oxazol-4-yl}-2-methoxypyridine obtained by Example 100-4 (542mg, 1.35mmol) in a similar manner to that of Example 31.

1H-NMR (300MHz, DMSO-d6) : δ 1.34(6H, d, J=7Hz), 3.05-3.20(1H, m), 3.87(3H, s), 6.82(2H, d, J=9Hz), 6.86(1H, d, J=9Hz), 7.34(2H, d, J=9Hz), 7.80(1H, dd, J=9,2Hz), 8.32(1H, d, J=2Hz), 9.91(1H, br peak).

MS (ES+) : 311.22.

Example 102

2-{4-[2-Isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol

The title compound (385mg, 84.3%) was prepared as a powder from 4-[2-isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenol obtained by Example 101 (400mg, 1.29mmol) and chloroethanol (623mg, 7.73mmol) in a similar manner to that of Example 87.

1H-NMR (300MHz, $CDCl_3$) : δ 1.42(6H, d, J=7Hz), 2.02(1H, t, J=6Hz), 3.09-3.22(1H, m), 3.96(3H, s), 3.96-4.01(2H, m), 4.10(2H, t, J=5Hz), 6.74(1H, d, J=9Hz), 6.91(2H, d, J=9Hz), 7.48(2H, d, J=9Hz), 7.81(1H, dd, J=9,2Hz), 8.40(1H, d, J=2Hz).
MS (ES+) : 355.24.

Example 103

2-{4-[2-Isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate

The title compound (400mg, 99.9%) was prepared as an oil from 2-{4-[2-isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 102 (328mg, 0.926mmol) in a similar manner to that of Example 34.

1H-NMR (300MHz, $CDCl_3$) : δ 1.43(6H, d, J=7Hz), 3.11(3H, s), 3.11-3.22(1H, m), 3.96(3H, s), 4.23-4.30(2H, m), 4.54-4.61(2H, m), 6.76(1H, d, J=9Hz), 6.90(2H, d, J=9Hz), 7.49(2H, d, J=9Hz), 7.82(1H, dd, J=9,2Hz), 8.39(1H, d, J=2Hz).

Example 104

2-(2-{4-[2-Isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

The title compound (355mg, 79.4%) was prepared as a powder from 2-{4-[2-isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 103 (400mg, 0.925mmol) and potassium phthalimide (257mg, 1.39mmol) in a similar manner to that of Example 35.

1H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.06-3.20(1H, m), 3.94(3H, s), 4.12(2H, t, J=5Hz), 4.25(2H, t, J=5Hz), 6.73(1H, d, J=9Hz), 6.86(2H, d, J=9Hz), 7.43(2H, d, J=9Hz), 7.69-7.80(3H, m), 7.80-7.93(2H, m), 8.36(1H, d, J=2Hz).
MS (ES+) : 484.17.

Example 105

2-{4-[2-Isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine

The title compound (327mg, 127%) was prepared as an an oil from 2-(2-{4-[2-isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 104 (353mg, 0.73mmol) in a similar manner to that of Example 36.

1H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.05-3.21(3H, m), 3.95(3H, s), 4.00(2H, t, J=5Hz), 6.75(1H, d, J=9Hz), 6.90(2H, d, J=9Hz), 7.46(2H, d, J=9Hz), 7.81(1H,

dd, J=9,2Hz), 8.40(1H, d, J=2Hz).
MS (ES+) : 354.21.

Example 106

N-(2-{4-[2-Isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (67mg, 54.9%) was prepared as a powder from 2-{4-[2-isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 105 (100mg, 0.283mmol) in a similar manner to that of Example 38.

1H-NMR (300MHz, $CDCl_3$) : δ 1.41(6H, d, J=7Hz), 3.04(3H, s), 3.10-3.21(1H, m), 3.56(2H, q, J=5Hz), 3.96(3H, s), 4.12(2H, t, J=5Hz), 4.76(1H, br peak), 6.75(1H, d, J=9Hz), 6.88(2H, d, J=9Hz), 7.49(2H, d, J=9Hz), 7.81(1H, dd, J=9,2Hz), 8.39(1H, d, J=2Hz).
MS (ES+) : 432.19.

Example 107

N-(2-{4-[2-Isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound (121mg, 61.3%) was prepared as a powder from 2-{4-[2-isopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 106 (176mg, 0.498mmol) in a similar manner to that of Example 18.

1H-NMR (300MHz, $CDCl_3$) : δ 1.42(6H, d, J=7Hz), 3.09-3.21(1H, m), 3.61(2H, q, J=5Hz), 3.95(3H, s), 4.06(2H, t, J=5Hz), 4.42(2H, br-s), 5.00(1H, br peak), 6.75(1H, d, J=9Hz), 6.88(2H, d, J=9Hz), 7.46(2H, d, J=9Hz), 7.82(1H, dd, J=9,2Hz), 8.38(1H, d, J=2Hz).
MS (ES+) : 397.18.

Example 108-1
2-[4-(Benzyloxy)phenyl]-2-bromo-1-(4-methoxyphenyl)ethanone

The title compound (10g, 101%) was prepared as an oil from 2-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)ethanone (8.0g, 24.1mmol) in a similar manner to that of Example 78-3.

1H-NMR (300MHz, $CDCl_3$) : δ 3.86(3H, s), 5.05(2H, s), 6.37(1H, s), 6.90(2H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.27-7.50(7H, m), 7.96(2H, d, J=9Hz).

Example 108-2
1-[4-(Benzyloxy)phenyl]-2-(4-methoxyphenyl)-2-oxoethyl cyclopropanecarboxylate

The title compound (1.68g, 83%) was prepared as an oil from 2-[4-(benzyloxy)phenyl]-2-bromo-1-(4-methoxyphenyl)ethanone obtained by Example 108-1 (2.0g, 4.86mmol) and cyclopropanecarboxylic acid (419mg, 4.86mmol) in a similar manner to that of Example 78-4.

1H-NMR (300MHz, $CDCl_3$) : δ 0.85-0.96(2H, m), 1.01-1.11(2H, m), 1.71-1.85(1H, m), 3.82(3H, s), 5.03(2H, s), 6.80(1H, s), 6.86(2H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.26-7.44(7H, m), 7.91(2H, d, J=9Hz).

Example 108-3

5-[4-(Benzyloxy)phenyl]-2-cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazole

The title compound (1.28g, 80.8%) was prepared as an oil from 1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)-2-oxoethyl cyclopropanecarboxylate obtained by Example 108-2 (1.66g, 3.99mmol) and ammonium acetate (2.46g, 31.9mmol) in a similar manner to that of Example 64-2.

1H-NMR (300MHz, $CDCl_3$) : δ 1.00-1.11(2H, m), 1.11-1.19(2H, m), 2.05-2.17(1H, m), 3.83(3H, s), 5.08(2H, s), 6.87(2H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.30-7.49(7H, m), 7.54(2H, d, J=9Hz)

MS (ES+) : 398.18

Example 109

4-[2-Cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl] phenol

The title compound (912mg, 94.4%) was prepared as a powder from 5-[4-(benzyloxy)phenyl]-2-cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazole Example 108-3 (1.25g, 3.14mmol) in a similar manner to that of Example 31.

1H-NMR (300MHz, $CDCl_3$) : δ 1.00-1.11(2H, m), 1.11-1.19(2H, m), 2.05-2.18(1H, m), 3.82(3H, s), 5.13(1H, br-s), 6.80(2H, d, J=9Hz), 6.88(2H, d, J=9Hz), 7.40(2H, d, J=9Hz), 7.53(2H, d, J=9Hz).

MS (ES+) : 308.18.

Example 110

2-{4-[2-Cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethanol

The title compound (765mg, 74.3%) was prepared as a powder from 4-[2-cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol obtained by Example 109 (900mg, 2.93mmol) and 2-chloroethanol (1.41g, 17.6mmol) in a similar manner to that of Example 87.

1H-NMR (300MHz, DMSO-d6) : δ 0.97-1.13(4H, m), 2.18-2.21(1H, m), 3.71(2H, q, J=5Hz), 3.77(3H, s), 4.00(2H, t, J=5Hz), 4.89(1H, t, J=5.5Hz) ,6.93(2H, d, J=9Hz), 6.98(2H, d, J=9Hz), 7.41(2H, d, J=9Hz), 7.95(2H, d, J=9Hz).

MS (ES+) : 352.20.

Example 111

2-{4-[2-Cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate

The title compound (308 mg, 100%) was prepared as an oil from 2-{4-[2-cyclopropyl-4-(4-methoxyphenyl)-1,

3-oxazol-5-yl]phenoxy}ethanol obtained by Example 110 (250mg, 0.711mmol) in a similar manner to that of Example 34.

1H-NMR (300MHz, $CDCl_3$) : δ 1.00-1.12(2H, m), 1.12-1.20(2H, m), 2.06-2.19(1H, m), 3.10(3H, s), 3.83(3H, s), 4.23-4.30(2H, m), 4.55-4.61(2H, m), 6.83-6.91(4H, m), 7.46(2H, d, J=9Hz), 7.51(2H, d, J=9Hz).

Example 112

2-(2-{4-[2-Cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

The title compound (237mg, 68.8%) was prepared as a powder from 2-{4-[2-cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 111 (308mg, 0.717mmol) and potassium phthalimide (199mg, 1.08mmol) in a similar manner to that of Example 35.

1H-NMR (300MHz, DMSO-d6) : δ 0.97-1.09(4H, m), 2.06-2.21(1H, m), 3.76(3H, s), 3.96(2H, t, J=6Hz), 4.25(2H, t, J=6Hz), 6.89-6.99(4H, m), 7.38(2H, d, J=9Hz), 7.42(2H, d, J=9Hz), 7.81-7.94(4H, m).

MS (ES+) : 481.17.

Example 113

2-{4-[2-Cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylamine

The title compound (201mg, 119%) was prepared as an oil from 2-(2-{4-[2-cyclopropyl-4-(4-methoxypheny l)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2 H)-dione obtained by Example 112 (233mg, 0.482mmol) in a similar manner to that of Example 36.

1H-NMR (300MHz, $CDCl_3$) : δ 1.00-1.11(2H, m), 1.11-1.20(2H, m), 2.05-2.18(1H, m), 3.09(2H, t, J=5Hz), 3.93(3H, s), 4.01(2H, d, J=5Hz), 6.81-6.92(4H, m), 7.45(2H, d, J=9Hz), 7.53(2H, d, J=9Hz).

Example 114

N-(2-{4-[2-Cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol -5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (64 mg, 69.8%) was prepared as an oil from 2-{4-[2-cyclopropyl-4-(4-methoxyphenyl)-1, 3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 113 (75mg, 0.214mmol) in a similar manner to that of E xample 38.

1H-NMR (300MHz, $CDCl_3$) : δ 1.01-1.11(2H, m), 1.11-1.20(2H, m), 2.04-2.18(1H, m), 3.03(3H, s), 3.56(2H, q, J=5Hz), 3.80(3H, s), 4.12(2H, t, J=5Hz), 4.75(1H, br peak), 6.85(2H, d, J=9Hz), 6.89(2H, d, J=9Hz), 7.46(2H, d, J=9Hz), 7.52(2H, d, J=9Hz).

Example 115

N-(2-{4-[2-Cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol -5-yl]phenoxy}ethyl)urea

The title compound (94mg, 66.4%) was prepared as a powder from 2-{4-[2-cyclopropyl-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 113 (126mg, 0.36mmol) in a similar manner to that of Example 18.

1H-NMR (300MHz, DMSO-d6) : δ 0.96-1.11(4H, m), 2.09-2.20(1H, m), 3.26-3.36(2H, m), 3.76(3H, s), 3.96(2H, t, J=5Hz), 5.564(2H, s), 6.66(1H, t, J=5Hz), 6.94(2H, d, J=9Hz), 7.00(2H, d, J=9Hz), 7.41(2H, d, J=9Hz), 7.45(2H, d, J=9Hz).
MS (ES+) : 394.21.

Example 116-1
1-[4-(Benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)-2-oxoethyl cyclopropanecarboxylate

The title compound (1.72g, 93.8%) was prepared as an oil from 2-[4-(benzyloxy)phenyl]-2-bromo-1-(6-methoxy-3-pyridinyl)ethanone (1.85g, 4.39mmol) and cyclopropanecarboxylic acid (378mg, 4.39mmol) in a similar manner to that of Example 78-4.

1H-NMR (300MHz, $CDCl_3$) : δ 0.85-0.99(2H, m), 1.04-1.14(2H, m), 1.71-1.85(1H, m), 3.96(3H, s), 5.04(2H, s), 6.70(1H, s), 6.73(1H, d, J=9Hz), 6.97(2H, d, J=9Hz), 7.28-7.45(7H, m), 8.10(1H, dd, J=9,2Hz), 8.78(1H, d, J=2Hz).
MS (ES+) : 418.18.

Example 116-2

5-{5-[4-(Benzyloxy)phenyl]-2-cyclopropyl-1,3-oxazol-4-yl}-2-methoxypyridine

The title compound (1.14g, 69.4%) was prepared as a powder from 1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)-2-oxoethyl cyclopropanecarboxylate obtained by Example 116-1 (1.72g, 4.12mmol) and ammonium acetate (2.54g, 33mmol) in a similar manner to that of Example 64-2.

1H-NMR (300MHz, $CDCl_3$) : δ 1.03-1.11(2H, m), 1.11-1.20(2H, m), 2.06-2.19(1H, m), 3.95(3H, s), 5.08(2H, s), 6.74(1H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.30-7.48(7H, m), 7.80(1H, dd, J=8,2Hz), 8.39(1H, d, J=2 Hz).
MS (ES+) : 399.17.

Example 117

4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenol

The title compound (710mg, 83.4%) was prepared as a powder from 5-{5-[4-(benzyloxy)phenyl]-2-cyclopropyl-1,3-oxazol-4-yl}-2-methoxypyridine obtained by Example 116-2 (1.1g, 2.76mmol) in a similar manner to that of Example 31.

1H-NMR (300MHz, $CDCl_3$) : δ 1.01-1.11(2H, m), 1.11-1.20(2H, m), 2.06-2.18(1H, m), 3.95(3H, s), 6.16(1H, br peak), 6.75(1H, d, J=9Hz), 6.81(2H, d, J=9Hz), 7.38 (2H, d, J=9Hz),

7.84(1H, dd, J=9,2Hz), 8.38(1H, d, J=2Hz).
MS (ES+) : 309.14.

Example 118

2-{4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol

The title compound (575mg, 71.9%) was prepared as a powder from 4-[2-cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenol obtained by Example 117 (700mg, 2.27mmol) and 2-chloroethanol (1.1 g, 13.6 mmol) in a similar manner to that of Example 87.

1H-NMR (300MHz, $CDCl_3$) : δ 1.02-1.11(2H, m), 1.11-1.20(2H, m), 2.02(1H, t, J=6Hz), 2.06-2.17(1H, m), 3.95(3H, s), 3.98(2H, t, J=5Hz), 4.10(2H, t, J=5Hz), 6.74(1H, d, J=9Hz), 6.90(2H, d, J=9Hz), 7.44(2H, d, J=9Hz), 7.79(1H, dd, J=9,2Hz), 8.38(1H, d, J=2Hz).
MS (ES+) : 353.19.

Example 119

2-{4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate

The title compound (310mg, 102%) was prepared as an oil from 2-{4-[2-cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethanol obtained by Example 118 (250mg, 0.709mmol) in a similar manner to that of Exampl 34.

1H-NMR (300MHz, $CDCl_3$) : δ 1.04-1.13(2H, m), 1.13-1.21(2H, m), 2.08-2.20(1H, m), 3.11(3H, s), 3.97(3H, s), 4.22-4.30(2H, m), 4.55-4.61(2H, m), 6.76(1H, d, J=9Hz), 6.89(2H, d, J=9Hz), 7.45(2H, d, J=9Hz), 7.82(1H, dd, J=9,2Hz), 8.39(1H, d, J=2Hz).
MS (ES+) : 431.11.

Example 120

2-(2-{4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione

The title compound (256mg, 73.8%) was prepared as a powder from 2-{4-[2-cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl methanesulfonate obtained by Example 119 (310mg, 0.72mmol) and potassium phthalimide (200mg, 1.08mmol) in a similar manner to that of Example 35.

1H-NMR (300MHz, DMSO-d6) : δ 1.00-1.12(4H, m), 2.11-2.23(1H, m), 3.86(3H, s), 3.97(2H, t, J=5Hz), 4.26(2H, t, J=5Hz), 6.84(1H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.39(2H, d, J=9Hz), 7.75(1H, dd, J=9,2Hz), 7.80-7.94(4H, m), 8.28(1H, d, J=2 Hz).
MS (ES+) : 482.16.

Example 121

2-{4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine

The title compound (220mg, 121%) was prepared as

an oil from 2-(2-{4-[2-cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 120 (250mg, 0.519mmol) in a similar manner to that of Example 36.

1H-NMR (300MHz, $CDCl_3$) : δ 1.00-1.11(2H, m), 1.11-1.20(2H, m), 2.06-2.19(1H, m), 3.10(2H, t, J=5Hz), 3.95(3H, s), 4.00(2H, t, J=5Hz), 6.74(1H, d, J=9Hz), 6.89(2H, d, J=9Hz), 7.44(2H, d, J=9Hz), 7.79(1H, dd, J=9,2Hz), 8.39(1H, d, J=2Hz).
MS (ES+) : 352.22.

Example 122

N-(2-{4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (57mg, 51.8%) was prepared as a powder from 2-{4-[2-cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 121 (90mg, 0.256mmol) in a similar manner to that of Example 38.

1H-NMR (300MHz, $CDCl_3$) : δ 1.03-1.12(2H, m), 1.12-1.21(2H, m), 2.06-2.19(1H, m), 3.04(3H, s), 3.50-3.60(2H, m), 3.95(3H, s), 4.11(2H, t, J=5Hz), 4.76(1H, br peak), 6.75(1H, d, J=9Hz), 6.86(2H, d, J=9Hz), 7.45(2H, d, J=9Hz), 7.80(1H, dd, J=9,2Hz), 8.38(1H, d, J=2Hz).
MS (ES+) : 430.10.

Example 123

N-(2-{4-[2-Cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound (63mg, 43.2%) was prepared as a powder from 2-{4-[2-cyclopropyl-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylamine obtained by Example 121 (130mg, 0.37mmol) in a similar manner to that of Example 18.

1H-NMR (300MHz, DMSO-d6) : δ 0.99-1.15(4H, m), 2.12-2.24(1H, m), 3.29-3.39(2H, m), 3.87(3H, s), 3.97(2H, t, J=5Hz), 5.54(2H, br-s), 6.16(1H, t, J=5Hz), 6.86(1H, d, J=9Hz), 7.01(2H, d, J=9Hz), 7.42(2H, d, J=9Hz), 7.78(1H, dd, J=9,2Hz), 8.31(1H, d, J=2Hz).

MS (ES+) : 395.17.

Example 124-1

1-[4-(Benzyloxy)phenyl]-2-(4-methoxyphenyl)-2-oxoethyl (acetyloxy)acetate

The title compound (8.75g, 100%) was prepared as an oil from 2-[4-(benzyloxy)phenyl]-2-bromo-1-(4-methoxyphenyl)ethanone (8.3g, 19.5mmol) and acetoxyacetic acid (2.3g, 19.5 mmol) in a similar manner to that of Example 78-4.

1H-NMR (300MHz, $CDCl_3$) : δ 2.14(3H, s), 3.82(3H, s), 4.72(1H, d, J=16Hz), 4.80(1H, d, J=16Hz), 5.02(2H, s), 6.80-6.90(3H, m), 6.95(2H, d, J=9Hz), 7.28-7.43(7H, m), 7.89(2H, d, J=9Hz).

Example 124-2

[5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methanol

The title compound (4.88g, 64.6%) was prepared as a powder from 1-[4-(benzyloxy)phenyl]-2-(4-methoxyphenyl)-2-oxoethyl (acetyloxy)acetate obtained by Example 124-1 (8.75g, 19.5mmol) in a similar manner to that of Example 91-7.

1H-NMR (300MHz, $CDCl_3$) : δ 3.84(3H, s), 4.78(2H, s), 5.08(2H, s), 6.90(2H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.29-7.46(5H, m), 7.50(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).

Example 125

5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carbaldehyde

The title compound (3.08g, 63.4%) was prepared as a powder from [5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]methanol obtained by Example 124-2 (4.88g, 12.6mmol) in a similar manner to that of Example 71.

H-NMR (300MHz, $CDCl_3$) : δ 3.87(3H, s), 5.11(2H, s), 6.95(2H, d, J=9Hz), 7.00(2H, d, J=9Hz), 7.30-7.50(5H, m), 7.60(2H, d, J=9Hz), 7.65(2H, d, J=9Hz), 9.76(1H, s).

Example 126

1-[5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanol

The title compound (150mg, 26.9%) was prepared as an oil from [5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carbaldehyde obtained by Example 125 (500mg, 1.3mmol) and isopropylmagnesium bromide (0.7M solution in tetrahydrofuran, 2.78mL) in a similar manner to that of Example 72.

1H-NMR (300MHz, $CDCl_3$) : δ 0.98-1.07(6H, m), 2.15-2.34(1H, m), 3.83(3H, s), 4.59(1H, br peak), 5.08(2H, s), 6.90(2H, d, J=9Hz), 6.95(2H, d, J=9Hz), 7.29-7.45(5H, m), 7.50(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).
MS (ES+) : 430.19.

Example 127
4-[2-(1-Hydroxy-2-methylpropyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol

The title compound (231mg, 108%) was prepared as an oil from 1-[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanol obtained by Example 126 (270mg, 0.629mmol) in a similar manner to that of Example 31.

1H-NMR (300MHz, $CDCl_3$) : δ 0.99-1.08(6H, m), 2.15-2.31(1H, m), 2.74(1H, d, J=7Hz), 3.83(3H, s), 4.60(1H, t, J=7Hz), 5.41(1H, s), 6.82(2H, d, J=9Hz), 7.90(2H, d, J=9Hz), 7.45(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).

MS (ES+) : 340.19.

Example 128

1-[5-[4-(2-Hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanol

The title compound (126mg, 48.9%) was prepared as an oil from 4-[2-(1-hydroxy-2-methylpropyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol obtained by Example 127 (228mg, 0.672mmol) and 2-chloroethanol (325mg, 4.03mmol) in a similar manner to that of Example 87.

1H-NMR (300MHz, $CDCl_3$) : δ 1.00-1.10(6H, m), 2.00(1H, t, J=6Hz), 2.19-2.33(1H, m), 2.65(1H, d, J=6Hz), 3.84(3H, s), 3.96(2H, q, J=5Hz), 4.10(2H, t, J=5Hz), 4.60(1H, t, J=6Hz), 6.85-6.95(4H, m), 7.50(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).
MS (ES+) : 384.18.

Example 129

1-[5-[4-(2-Hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanone

The title compound (17mg, 13.6%) was prepared as an oil from 1-[5-[4-(2-hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-2-methyl-1-propanol obtained by Example 128 (126mg, 0.329mmol) in a similar manner to that of Example 71.

1H-NMR (300MHz, $CDCl_3$) : δ 1.29(6H, d, J=7Hz), 1.99(1H,

t-like), 3.70-3.83(1H, m), 3.86(3H, s), 3.95-4.04(2H, m), 4.12(2H, t, J=5Hz), 6.88-6.99(4H, m), 7.58(2H, d, J=9Hz), 7.62(2H, d, J=9Hz).

MS (ES+) : 382.13.

Example 130

1-[5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanol

The title compound (143mg, 24.9%) was prepared as an oil from [5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carbaldehyde obtained by Example 125 (500mg, 1.3mmol) and isobutylmagnesium bromide (2M solution in diethyl ether, 0.78mL) in a similar manner to that of Example 72.

1H-NMR (300MHz, $CDCl_3$) : δ 1.00(6H, d, J=7Hz), 1.74-1.99(3H, m), 2.50(1H, d, J=6Hz), 3.84(3H, s), 4.84-4.96(1H, m), 5.09(2H, s), 6.89(2H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.28-7.46(5H, m), 7.50(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).

MS (ES+) : 444.21.

Example 131

4-[2-(1-Hydroxy-3-methylbutyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol

The title compound (112mg, 99.7%) was prepared as an oil from 1-[5-[4-(b nzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanol obtained b

y Example 130 (141mg, 0.318mmol) in a similar manner t o that of Example 31.

1H-NMR (300MHz, $CDCl_3$) : δ 1.00(6H, d, J=7Hz), 1.76-1.96(3H, m), 2.59(1H, br peak), 3.83(3H, s), 4.85-4.95(1H, m), 5.37(1H, br peak), 6.81(2H, d, J=9Hz), 6.90(2H, d, J=9Hz), 7.44(2H, d, J=9Hz), 7.54(2H, d, J=9Hz).

MS (ES+) : 354.19.

Example 132

1-[5-[4-(2-Hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanol

The title compound (118mg, 95.4%) was prepared as an oil from 4-[2-(1-hydroxy-3-methylbutyl)-4-(4-methoxyphenyl)-1,3-oxazol-5-yl]phenol obtained by Example 131 (110mg, 0.311mmol) and 2-chloroethanol (150mg, 1.87mmol) in a similar manner to that of Example 87.

1H-NMR (300MHz, $CDCl_3$) : δ 1.01(6H, d, J=7Hz), 1.75-1.96(3H, m), 2.05(1H, br peak), 2.62(1H, br peak), 3.84(3H, s), 3.94-4.02(2H, m), 4.11(2H, t, J=5Hz), 4.90(1H, br peak), 6.85-6.95(4H, m), 7.50(2H, d, J=9Hz), 7.55(2H, d, J=9Hz).

MS (ES+) : 398.20.

Example 133

1-[5-[4-(2-Hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanone

The title compound (42.5mg, 36.8%) was prepared as an oil from 1-[5-[4-(2-hydroxyethoxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]-3-methyl-1-butanol obtained by Example 132 (116mg, 0.292mmol) in a similar manner to that of Example 71.

1H-NMR (300MHz, $CDCl_3$) : δ 1.04(6H, d, J=7Hz), 2.00(1H, t-like, J=5Hz), 2.30-2.46(1H, m), 3.00(2H, d, J=7Hz), 3.86(3H, s), 3.95-4.04(2H, m), 4.12(2H, t, J=5Hz), 6.88-6.99(4H, m), 7.59(2H, d, J=9Hz), 7.62(2H, d, J=9Hz).
MS (ES+) : 396.19.

Example 134

5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxylic acid

The title compound (1.05g, 100%) was prepared as an amorphous from 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carbaldehyde obtained by Example 125 (1.0g, 2.59mmol) in a similar manner to that of Example 74.

1H-NMR (300MHz, DMSO-d6) : δ 3.78(3H, s), 5.14(2H, s), 6.98(2H, d, J=9Hz), 7.10(2H, d, J=9Hz), 7.30-7.54(9H, m).
MS (ES-) : 400.19.

Example 135

5-[4-(Benzyloxy)phenyl]-N,N-diethyl-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

The title compound (132mg, 44.1%) was prepared as a powder from 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxylic acid obtained by Example 134 (263mg, 0.655mmol) and diethylamine (57.5mg, 0.786mmol) in a similar manner to that of Example 75.

1H-NMR (300MHz, $CDCl_3$) : δ 1.26(3H, t, J=7Hz), 1.35(3H, t), 3.57(2H, q, J=7Hz), 3.85(3H, s), 3.91(2H, q, J=7Hz), 5.09(2H, s), 6.90(2H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.30-7.46(5H, m), 7.54-7.64(4H, m).

Example 136

N,N-Diethyl-5-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide

The title compound (95mg, 91.1%) was prepared as a powder from 5-[4-(benzyloxy)phenyl]-N,N-diethyl-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 135 (130mg, 0.285mmol) in a similar manner to that of Example 31.

1H-NMR (300MHz, $CDCl_3$) : δ 1.30(3H, t, J=7Hz), 1.39(3H, t, J=7Hz), 3.61(2H, q, J=7Hz), 3.85(3H, s), 4.05(2H, q, J=7Hz), 6.91(2H, d, J=9Hz), 7.00(2H, d, J=9Hz), 7.45(2H, d, J=9Hz), 7.55-7.66(3H, m).
MS (ES+) : 367.20.

Example 137

N,N-Diethyl-5-[4-(2-hydroxyethoxy)phenyl]-4-(4-m thox

yphenyl)-1,3-oxazole-2-carboxamide

The title compound (58mg, 57.5%) was prepared as a powder from N,N-diethyl-5-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxamide obtained by Example 136 (90mg, 0.246mmol) and 2-chloroethanol (119mg, 1.47mmol) in a similar manner to that of Example 87.

1H-NMR (300MHz, DMSO-d6) : δ 1.16(3H, t, J=7Hz), 1.27(3H, t, J=7Hz), 3.46(2H, q, J=7Hz), 3.66-3.82(7H, m), 4.04(2H, t, J=5Hz), 4.90(1H, t, J=5Hz), 7.00(2H, d, J=9Hz), 7.05(2H, d, J=9Hz), 7.46-7.55(4H, m).
MS (ES+) : 411.19.

Example 138
1-{[5-[4-(Benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]carbonyl}piperidine

The title compound (185mg, 49.5%) was prepared as a powder from 5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazole-2-carboxylic acid obtained by Example 134 (320mg, 0.797mmol) and piperidine (81.5mg, 0.957mmol) in a similar manner to that of Example 75.

1H-NMR (300MHz, $CDCl_3$) : δ 1.61-1.78(6H, m), 3.69-3.79(2H, m), 3.84(3H, s), 4.04-4.13(2H, m), 5.09(2H, s), 6.91(2H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.30-7.48(5H, m), 7.54-7.64(4H, m).
MS (ES+) : 469.20.

Example 139

4-[4-(4-Methoxyphenyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenol

The title compound (138mg, 94.9%) was prepared as a powder from 1-{[5-[4-(benzyloxy)phenyl]-4-(4-methoxyphenyl)-1,3-oxazol-2-yl]carbonyl}piperidine obtained by Example 138 (180mg, 0.384mmol) in a similar manner to that of Example 31.

1H-NMR (300MHz, $CDCl_3$) : δ 1.64-1.76(6H, m), 3.72-3.82(2H, m), 3.84(3H, s), 4.16-4.26(2H, m), 6.90(2H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.24(1H, s), 7.45(2H, d, J=9Hz), 7.49(2H, d, J=9Hz).

MS (ES-) : 377.28.

Example 140

2-{4-[4-(4-Methoxyphenyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenoxy}ethanol

The title compound (96mg, 66.1%) was prepared as a powder from 4-[4-(4-methoxyphenyl)-2-(1-piperidinylcarbonyl)-1,3-oxazol-5-yl]phenol obtained by Example 139 (130mg, 0.344mmol) and 2-chloroethanol (166mg, 2.06mmol) in a similar manner to that of Example 87.

1H-NMR (300MHz, DMSO-d6) : δ 1.53-1.72(6H, m), 3.63(2H, t, J=5.5Hz), 3.72(2H, q, J=5Hz), 3.79(3H, s), 3.94(2H, t, J=5.5Hz), 4.04(2H, t, J=5Hz), 4.90(1H, t, J=5.5Hz), 7.00(2H, d, J=9Hz), 7.05(2H, d, J=9Hz), 7.46-7.55(4H, m).

MS (ES+) : 423.15.

Example 141-1

Ethyl {[2-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]amino}(oxo)acetate

The title compound (3.0g, 103%) was prepared from 2-amino-1-[4-(benzyloxy)phenyl]-2-(6-methoxy-3-pyridinyl)ethanone hydrochloride obtained by Example 30-5 in a similar manner to that of Example 1-1.

1H-NMR (300MHz,$CDCl_3$) : δ 1.37(3H, t, J=7Hz), 3.88(3H, s), 4.35(2H, q, J=7Hz), 5.10(2H, s), 6.41(1H, d, J=7Hz), 6.67(1H, d, J=8Hz), 6.97(2H, d, J=8Hz), 7.31-7.40(5H, m), 7.56(1H, dd, J=8,2Hz), 7.94(2H, d, J=8Hz), 8.27(1H, d, J=2Hz), 8.55(1H, d, J=7Hz).

Example 141-2

Ethyl 5-[4-(benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxylate

The title compound was prepared (2.3g, 82.6%) from ethyl {[2-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-2-oxoethyl]amino}(oxo)acetate obtained by Example 141-1 in a similar manner to that of Example 9-5.

1H-NMR (300MHz,$CDCl_3$) : δ 1.46(3H, t, J=7Hz), 3.97(3H, s), 4.52(2H, q, J=7Hz), 5.10(2H, s), 6.79(1H, d, J=8Hz), 7.00(2H, d, J=8Hz), 7.32-7.46(5H, m), 7.59(2H, d, J=8Hz), 7.86(1H, dd, J=8,2Hz), 8.44(1H, d, J=2 Hz).

MS (ES+) : 431.17.

Example 142

5-[4-(Benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide

To a solution of ethyl 5-[4-(benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxylate obtained by Example 141-2 (2.18g, 5.06mmol) in 80 ml of 1,4-dioxane at 0℃ was added 2M NH_3 in methanol (25mL, 50.6mmol). The clear solution was stirred for 30min at the same temperature and ammonia gas was bubbled for 5min. The reaction mixture was allowed to warm to room temperature and stirred for 3hrs.

The solution was evaporated to give the title compound (2.1g, quant.) as white crystals.

1H-NMR (300MHz,$CDCl_3$) : δ 3.98(3H, s), 5.10(2H, s), 5.75(1H, br-s), 6.79(1H, d, J=8Hz), 6.97(1H, br-s), 7.00(2H, d, J=8Hz), 7.34-7.45(5H, m), 7.59(2H, d, J=8Hz), 7.82(1H, dd, J=8,2Hz), 8.45(1H, d, J=2Hz).

MS (ES+) : 402.13.

Example 143

5-(4-Hydroxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide

The title compound was prepared (1.7g, 99.6%) from 5-[4-(benzyloxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide obtained by Example 142 in a

similar manner to that of Exampl 65.

1H-NMR (300MHz,DMSO-d6) : δ 3.89(3H, s), 6.87(2H, d, J=8Hz), 6.92(1H, d, J=8Hz), 7.44(2H, d, J=8Hz), 7.86(1H, dd, J=8,2Hz), 7.94(1H, br-s), 8.31(1H, br-s), 8.38(1H, d, J=2Hz).

MS (ES+) : 312.15.

Example 144

tert-Butyl 2-{4-[2-(aminocarbonyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylcarbamate

The title compound was prepared (2.1g, 98.5%) from 5-(4-hydroxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carboxamide obtained by Example 143 in a similar manner to that of Example 13.

1H-NMR (300MHz, $CDCl_3$) : δ 1.46(9H, s), 3.55(2H, m), 3.98(3H, s), 4.05(2H, t, J=5Hz), 5.02(1H, br), 5.83(1H, br-s), 6.79(1H, d, J=8Hz), 6.91(2H, d, J=8Hz), 6.99(1H, br-s), 7.58(2H, d, J=8Hz), 7.81(1H, dd, J=8,2Hz), 8.43(1H, d, J=2Hz).

MS (ES+) : 455.08.

Example 145

tert-Butyl 2-{4-[2-cyano-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethylcarbamate

The title compound was prepared (1.4g, 69.4%) from tert-Butyl 2-{4-[2-(aminocarbonyl)-4-(6-methoxy-3-p

yridinyl)-1,3-oxazol-5-yl]phenoxy}ethylcarbamate obta
ined by Example 144 in a similar manner to that of Exa
mple 23.

1H-NMR (300MHz, $CDCl_3$) : δ 1.46(9H, s), 3.56(2H, m), 3.
98(3H, s), 4.07(2H, t, J=5Hz), 4.98(1H, br), 6.80(1H,
d, J=8Hz), 6.94(2H, d, J=8Hz), 7.54(2H, d, J=8Hz), 7.8
0(1H, dd, J=8,2Hz), 8.42(1H, d, J=2Hz).
MS (ES+) : 437.09.

Example 146
5-[4-(2-Aminoethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)
-1,3-oxazole-2-carbonitrile

The title compound was prepared (1.3g, 108%) from
tert-butyl 2-{4-[2-cyano-4-(6-methoxy-3-pyridinyl)-1,
3-oxazol-5-yl]phenoxy}ethylcarbamate obtained by Exam
ple 145 in a similar manner to that of Example 17.

1H-NMR (300MHz, $CDCl_3$) : δ 3.10-3.14(2H, m), 3.89(1H,
br-s), 3.97(3H, s), 4.03(2H, m), 4.28(1H, br), 6.78(1H,
m), 6.98(2H, m), 7.54(2H, dd, J=8,2Hz), 7.80(1H, m),
8.43(1H, s).
MS (ES+) : 337.13.

Example 147
N-(2-{4-[2-Cyano-4-(6-methoxy-3-pyridinyl)-1,3-oxazol
-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound was prepared (20mg, 9.2%) from

5-[4-(2-aminoethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole-2-carbonitrile obtained by Example 146 in a similar manner to that of Example 38.

1H-NMR (300MHz, $CDCl_3$) : δ 3.04(3H, s), 3.55-3.61(2H, m), 3.98(3H, s), 4.16(2H, t, J=5Hz), 4.83(1H, br-t, J=5Hz), 6.81(1H, d, J=8Hz), 6.94(2H, d, J=8Hz), 7.56(2H, d, J=8Hz), 7.81(1H, dd, J=8,2Hz), 8.42(1H, d, J=2Hz).
MS (ES+) : 415.01.

Example 148

N-(2-{4-[2-Cyano-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-5-yl]phenoxy}ethyl)urea

The title compound was prepared as crystals (55mg, 79.7%) from 5-[4-(2-aminoethoxy)phenyl]-4-(6-methoxy-3-pyridinyl)-1,3-oxazole- 2-carbonitrile obtained by Example 147 in a similar manner to that of Example 18.

1H-NMR (300MHz, DMSO-d6) : δ 3.30-3.39(2H, m), 3.90(3H, s), 4.01(2H, t, J=5Hz), 5.55(2H, s), 6.18(1H, br-t, J=5Hz), 6.94(1H, d, J=8Hz), 7.10(2H, d, J=8Hz), 7.56(2H, d, J=8Hz), 7.85(1H, dd, J=8,2Hz), 8.38(1H, d, J=2Hz).
MS (ES+) : 380.09.

Example 149-1

1-(4-Methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl 2-hydroxy-2-methylpropanoate

The title compound (1.32g, 51.7%) was prepared from

2-(4-methoxyphenyl)-2-bromo-1-(6-m thoxy-3-pyridinyl) ethanone obtained and 2-hydroxy-2-methylpropionic acid in a similar manner to that of Example 78-4.

1H-NMR (300MHz, $CDCl_3$) : δ 1.48(3H, s), 1.59(3H, s), 1.67(1H, br-s), 3.79(3H, s), 3.96(3H, s), 6.72(1H, s), 6.74(1H, d, J=8.8Hz), 6.91(2H, d, J=8.8Hz), 7.37(2H, d, J=8.8Hz), 8.09(1H, dd, J=8.8,2.6Hz), 8.77(1H, d, J=2.6Hz).
MS (ES+) : 360.20.

Example 149-2

2-[5-(4-Methoxyphenyl)-4-(6-methoxy-3-pyridinyl)-1,3-oxazol-2-yl]-2-propanol

The title compound (175mg, 14%) was prepared from 1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridinyl)-2-oxoethyl 2-hydroxy-2-methylpropanoate obtained by Example 149-1 and ammonium acetate in a similar manner to that of Example 64-2.

1H-NMR (300MHz, $CDCl_3$) : δ 1.72(6H, s), 2.48(1H, br-s), 3.84(3H, s), 3.96(3H, s), 6.77(1H, d, J=8.4Hz), 6.92(2H, d, J=8.8Hz), 7.48(2H, d, J=8.8Hz), 7.84(1H, dd, J=8.4,2.6Hz), 8.43(1H, d, J=2.6Hz).
MS (ES+) : 341.18 (M+1).

In order to illustrate the usefulness of the object compounds (I), the pharmacological test data of the compounds (I) are shown in the following.

[A] ANALGESIC ACTIVITY :

Effect on adjuvant arthritis in rats :

(i) Test Method :

Analgesic activity of a single dose of agents in arthritic rats was studied.

Arthritis was induced by injection of 0.5 mg of Mycobacterium tuberculosis (Difco Laboratories, Detroit, Mich.) in 50μl of liquid paraffin into the right hind footpad of Lewis rats aged 7 weeks. Arthritic rats were randomized and grouped (n=10) for drug treatment based on pain threshold of left hind paws and body weight on day 22.

Drugs (Test compounds) were administered and the pain threshold was measured 2hrs after drug administration. The intensity of hyperalgesia was assessed by the method of Randall - Selitto. The mechanical pain threshold of the left hind paw (uninjected hind paw) was determined by compressing the ankle joint with a balance pressure apparatus (Ugo Basile Co.Ltd., Varese, Italy). The threshold pressure of rats squeaking or struggling was expressed in grams. The threshold pressure of rats treated with drugs was compared with that of non-treated rats. A dose showing the ratio of 1.5 is considered to be the effective dose.

(ii) Test Results:

Test compound (Example No.)	Dose (mg/kg)	The coefficient of analgesic
12	3.2	>1.5
33	3.2	>1.5
54	3.2	>1.5
55	3.2	>1.5
118	3.2	>1.5

[B] Inhibiting activity against COX-I and COX-II (Whole Blood Assay):

(i) Test Method :

Whole blood assay for COX-I

Fresh blood was collected by syringe without anticoagulants from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection.

500μl Aliquots of human whole blood were immediately incubated with 2μl of either dimethyl sulfoxide vehicle or a test compound at final concentrations for 1hr at 37℃ to allow the blood to clot. Appropriate treatments (no incubation) were used as blanks. At the end of the incubation, 5μl of 250mM Indomethacin was added to stop the reaction. The blood was centrifuged at 6000 x g for 5min at 4℃ to obtain serum. A 100μl aliquot of serum was mixed with 400μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4℃ and was assayed for TXB_2 using an enzyme immunoassay kit according to the manufacturer's procedure.

For a test compound, the results were expressed as percent inhibition of thromboxane B_2(TXB_2) production relative to control incubations containing dimethyl sulfoxide vehicle.

The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC_{50} value was calculated by least squares method.

Whole blood assay for COX-II

Fresh blood was collected in heparinized tubes by syringe from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection.

500㎕ aliquots of human whole blood were incubated with either 2㎕ dimethyl sulfoxide vehicle or 2㎕ of a test compound at final concentrations for 15 min at 37℃. This was followed by incubation of the blood with 10 ㎕ of 5mg/ml lipopolysaccharide for 24hrs at 37℃ for induction of COX-II. Appropriate PBS treatments (no LPS) were used as blanks. At the end of the incubation, the blood was centrifuged at 6000X g for 5 min at 4℃ to obtain plasma. A 100㎕ aliquot of plasma was mixed with 400 ㎕ methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000X g for 5min at 4℃ and was assayed for prostaglandin E_2 (PGE_2) using a radioimmunoassay kit after conversion of PGE_2 to its methyl oximate derivative according to the manufacturer's procedure.

For a test compound, the results were expressed as

percent inhibition of PGE_2 production relative to control incubations containing dimethyl sulfoxide vehicle. The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC_{50} value was calculated by least squares method.

(ii) Test Results:

Test Compound (Example No.)	COX-I IC50 (μM)	COX-II IC50 (μM)
12	< 0.01	> 0.1
33	< 0.01	> 0.1
54	< 0.01	> 0.1
55	< 0.01	> 0.1
118	< 0.01	> 0.1

It appeared, from the above-mentioned Test Results, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against COX, particularly a selective inhibiting activity against COX-I.

[C] Inhibiting activity on aggregation of platelet

(i) Methods

Preparation of platelet-rich plasma

Blood from healthy human volunteers was collected into plastic vessels containing 3.8% sodium citrate (1/10 volume). The subject had no taken any compounds for at least 7days prior to blood collection. Platelet-rich plasma was obtained from the supernatant fraction of blood

after centrifugation at 1200rpm. for 10min. Platelet-poor plasma was obtained by centrifugation of the remaining blood at 3000rpm for 10min.

Measurement of platelet aggregation

Platelet aggregation was measured according to the turbidimetric method with an aggregometer (Hema Tracer). In the cuvette, platelet-rich plasma was pre-incubated for 2min at 37℃ after the addition of compounds or vehicle. In order to quantify the inhibitory effects of each compound, the maximum increase in light transmission was determined from the aggregation curve for 7min after the addition of agonist. We used collagen as agonist of platelet aggregation in this study. The final concentration of collagen was 0.5μg/mL. The effect of each compound was expressed as percentage inhibition agonist-induced platelet aggregation compared with vehicle treatment. Data are presented as the mean ± S.E.M. for six experiments. The IC_{50} value was obtained by linear regression, and is expressed as the compound concentration required to produce 50% inhibition of agonist-induced platelet aggregation in comparison to vehicle treatment.

It appeared, from the above-mentioned Test Result, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against platelet aggregation. Therefore, the compound (I) or pharmaceutically acceptable salts thereof are useful for preventing or treating disorders induced by platelet aggregation, such as thrombosis.

Additionally, it was further confirmed that the compounds (I) of the present invention lack undesired side-effects of non-selective NSAIDs, such as gastrointestinal disorders, bleeding, renal toxicity, cardiovascular affection, etc.

As shown above, the object compound (I) or pharmaceutically acceptable salts thereof of this invention possesses COX inhibiting activity and possesses strong anti-inflammatory, antipyretic, analgesic, antithrombotic, anti-cancer activities, and so on.

The object compound (I) and pharmaceutically acceptable salt thereof, therefore, are useful for treating and/or preventing COX mediated diseases, inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals by using administered systemically or topically.

More particularly, the object compound (I) and pharmaceutically acceptable salts thereof are useful for treating and/or preventing inflammation and acute or chronic pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, scapulohumeral periarthritis, cervical syndrome, etc.]; lumbago; inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.]; inflammatory eye condition [e.g. conjunctivitis, etc.]; lung disorder in which

inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.]; condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varioloid, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.]; gingivitis; menorrhalgia; inflammation, pain and tumescence after operation or injury [pain after odontectomy, etc.]; pyrexia, pain and other conditions associated with inflammation, particularly those in which lipoxygenase and cyclooxygenase products are a factor, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, or the like.

Additionally, the object compound (I) or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular diseases, the diseases caused by hyperglycemia and hyperlipemia.

The object compound (I) and a salt thereof can be used for prophylactic and therapeutic treatment of arterial thrombosis, arterial sclerosis, ischemic heart diseases [e.g. angina pectoris (e.g. stable angina pectoris, unstable angina pectoris including imminent infarction, etc.), myocardial infarction (e.g. acute myocardial infarction, etc.), coronary thrombosis, etc.],

ischemic brain diseases [e.g. cerebral infarction (e.g. acute cerebral thrombosis, etc.), cerebral thrombosis (e.g. cerebral embolism, etc.), transient cerebral ischemia (e.g. transient ischemic attack, etc.), cerebrovascular spasm after cerebral hemorrhage(e.g. cerebrovascular spasm after subarachnoid hemorrhage, etc.), etc.], pulmonary vascular diseases (e.g. pulmonary thrombosis, pulmonary embolism etc.), peripheral circulatory disorder [e.g. arteriosclerosis obliterans, thromboangiitis obliterans (i.e. Buerger's disease), Raynaud's disease, complication of diabetes mellitus (e.g. diabetic angiopathy, diabetic neuropathy, etc.), phiebothrombosis (e.g. deep vein thrombosis, etc.), etc.], complication of tumors (e.g. compression thrombosis), abortion [e.g. placental thrombosis, etc.], restenosis and reocclusion [e.g. restenosis and/or reocclusion after percutaneous transluminal coronary angioplasty (PTCA), restenosis and reocclusion after the administration of thrombolytic drug (e.g. tissue plasminogen activator (TPA), etc.)], thrombus formation in case of vascular surgery, valve replacement, extracorporeal circulation [e.g. surgery (e.g. open heart surgery, pump-oxygenator, etc.) hemodialysis, etc.] or transplantation, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia, essential thrombocytosis, inflammation (e.g. nephritis, etc.), immune diseases, atrophic thrombosis, creeping thrombosis, dilation thrombosis, jumping thrombosis, mural thrombosis, etc..

The object compound (I) and a salt thereof can be used for the adjuvant therapy with thrombolytic drug (e.g.

TPA, etc.) or anticoagulant (e.g. heparin, etc.).

And, the compound (I) is also useful for inhibition of thrombosis during extra corporeal circulation such as dialysis.

Particularly, the following diseases are exemplified:

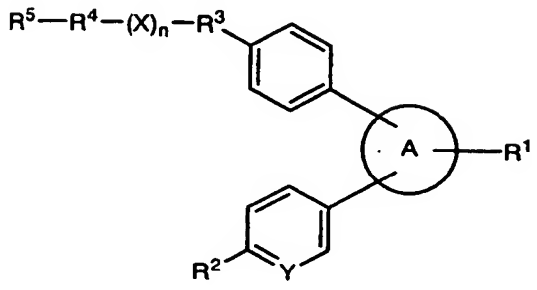
pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, juvenile arthritis, etc; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury; etc..

And on the commercial package comprising the pharmaceutical composition mentioned above, the matter, which states above mentioned effects, may be written.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula (I):



(I)

wherein

R^1 is (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkyl substituted with substituent(s) (i) described later, [(lower)alkoxy]carbonyl, carbamoyl, carbamoyl substituted with substituent(s) (ii) described later, cyano, (lower)acyl, aryl, aryl carbonyl, carboxy, or cycloalkyl;

R^2 is (lower)alkyl, (lower)alkoxy, cyano, or heterocyclic group;

R^3 is (lower)alkylene, (lower)alkenylene, or covalent bond;

R^4 is (lower)alkylene, (lower)alkenylene, or covalent bond;

R^5 is hydrogen, aryl, hydroxy, [(lower)alkoxy]carbonyl, cyano, amino, [(lower)acyl]amino, [(lower)alkoxy]carbonylamino, carbamoylamino, [(lower)acyl]oxy, [(lower)alkyl]sulfonyloxy, heteroaryl, or

[(lower)alkyl]sulfonylamino;

X is "O", "S", "SO", or "SO_2";

Y is "CH" or "N";

n is 0 or 1;

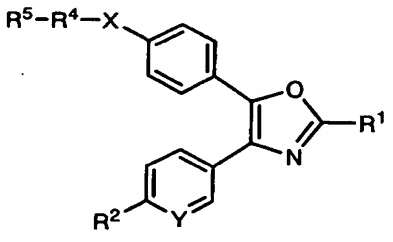
is oxazolyl group;

substituent(s) (i) is(are) selected from the group consisting of (lower)alkoxy, hydroxy, halogen, aryl[(lower)alkyl]oxy, [(lower)alkoxy]carbonyl, carboxy, [(lower)acyl]oxy, and aryl; and

substituent(s) (ii) is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, and in case that carbamoyl is substituted with two (lower)alkyls they may be cyclized together;

or pharmaceutically acceptable salts thereof.

2. A compound of the formula (Ia):



(Ia)

wherein

R^1 is (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkyl substituted with substituent(s) (i) described later, [(lower)alkoxy]carbonyl, carbamoyl, carbamoyl substituted with substituent(s) (ii) described later, cyano,

(lower)acyl, aryl, aryl carbonyl, carboxy, or cycloalkyl;

R^2 is (lower)alkyl, (lower)alkoxy, cyano, or heterocyclic group,

R^4 is (lower)alkylene, (lower)alkenylene, or covalent bond;

R^5 is hydrogen, aryl, hydroxy, [(lower)alkoxy]carbonyl, cyano, amino, [(lower)acyl]amino, [(lower)alkoxy]carbonylamino, carbamoylamino, [(lower)acyl]oxy, [(lower)alkyl]sulfonyloxy, heteroaryl, or [(lower)alkyl]sulfonylamino;

X is "O", "S", "SO", or "SO_2";

Y is "CH" or "N";

substituent(s) (i) is(are) selected from the group consisting of (lower)alkoxy, hydroxy, halogen, aryl[(lower)alkyl]oxy, [(lower)alkoxy]carbonyl, carboxy, [(lower)acyl]oxy, and aryl; and

substituent(s) (ii) is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, and in case that carbamoyl is substituted with two substituents they may be cyclized together;

or pharmaceutically acceptable salts thereof.

3. A compound of Claim 1 or 2 for use as a medicament.

4. The compound of Claim 3 for use in the treatment and/or prevention of inflammatory conditions, various pains,

collagen diseases, autoimmune diseases, various immunity diseases, thrombosis, cancer or neurodegerative diseases in human beings or animals.

5. A medicament comprising a compound of Claim 1 or 2 as an active ingredient.

6. A pharmaceutical composition comprising a compound of Claim 1 or 2 as an active ingredient, in association with a pharmaceutically acceptable carrier or excipient.

7. A method for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases which comprises administering an effective amount of the compound of Claim 1 or 2 to human beings or animals.

8. Use of the compound of Claim 1 or 2 for the manufacture of a medicament for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases in human beings or animals.

9. The analgesic agent comprising the compound of Claim 1 or 2, which is usable for treating and/or preventing pains caused by or associated with acute or chronic inflammations.

10. The analgesic agent of Claim 8, which is usable for treating or preventing pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, juvenile arthritis; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury.

11. A commercial package comprising the pharmaceutical composition containing the compound (I) identified in Claim 1 or 2 and a written matter associated therewith, wherein the written matter states that the compound (I) can or should be used for preventing or treating inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases.

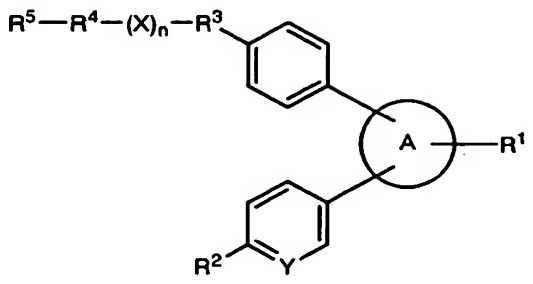
DATED this 31st day of March, 2003

Fujisawa Pharmaceutical Co., Ltd.

By DAVIES COLLISON CAVE
Patent Attorneys for the Applicant

A B S T R A C T

A compound of the formula (I):



(I)

wherein

R^1 is cycloalkyl, etc;

R^2 is (lower)alkoxy, etc;

R^3 is (lower)alkylene, etc;

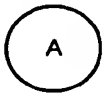
R^4 is (lower)alkylene, etc;

R^5 is hydroxy, etc;

X is "O", "S", "SO", or "SO_2";

Y is "CH" or "N";

n is 0 or 1;



is oxazolyl group;

or pharmaceutically acceptable salts thereof, which are useful as a medicament.

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